A 48-year-old woman comes to the emergency department with headache, dizziness, and nausea for the past several hours. She has no fever, nasal congestion, or cough but reports that her husband has also been complaining of headache. The patient has been burning wood in the fireplace to warm her house after losing electricity during a snowstorm. Her temperature is 37 C (98.6 F), blood pressure is 135/70 mm Hg, and pulse is 94/min and regular. Physical examination is unremarkable. The substance responsible for this patient's condition most likely impairs hemoglobin function through which of the following mechanisms?

- A. Alteration of the partial pressure of oxygen
- B. Competitive binding to heme
- C. Deactivation of a reductase enzyme
- D. Denaturation of the globin chains
- E. Irreversible linking to heme
- F. Oxidation of the porphyrin ring

Submit

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- A. Alteration of the partial pressure of oxygen (1%)
- ✓ B. Competitive binding to heme (86%)
- C. Deactivation of a reductase enzyme (1%)
- D. Denaturation of the globin chains (0%)
- E. Irreversible linking to heme (9%)
- F. Oxidation of the porphyrin ring (0%)

Omitted
Correct answer
B

86%
Answered correctly

03 secs
Time Spent

04/26/2020
Last Updated

Explanation

This patient most likely has **carbon monoxide (CO) poisoning**, a condition that presents with nonspecific findings ranging from headache and dizziness to convulsions and respiratory arrest depending on concentration and exposure. CO is a colorless, odorless, tasteless gas that is a byproduct of incomplete hydrocarbon combustion. CO poisoning is most often caused by smoke inhalation from a fire or the burning of fuel

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CO toxicity occurs because of CO's ability to competitively bind iron present in heme proteins. The gas binds to heme iron with a much higher affinity than oxygen, forming **carboxyhemoglobin**. Even if only 1 of the 4 heme sites is affected, the remaining 3 heme groups have **increased oxygen affinity** (leftward shift of the oxygen dissociation curve), impeding oxygen delivery to tissues. CO is also capable of binding cardiac myoglobin with high affinity, disrupting the heart's ability to use oxygen and thereby decreasing cardiac output. At a cellular level, CO binds to cytochrome oxidase, inhibiting aerobic metabolism and exacerbating tissue hypoxia.

Treatment for CO poisoning is administration of **high-flow or hyperbaric oxygen** therapy as this hastens the dissociation of CO from carboxyhemoglobin.

(Choice A) The partial pressure of oxygen (pO_2) is a measure of dissolved oxygen in the plasma, the amount of which does not change in CO poisoning.

(Choice C) NADH methemoglobin reductase reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), regenerating hemoglobin from methemoglobin. Enzyme deficiency results in congenital methemoglobinemia.

(Choice D) Globin chain denaturation occurs in G6PD-deficient red blood cells when oxidant stressors cause sulfhydryl group cross-linking.

(Choice E) CO reversibly binds hemoglobin at its heme moieties.

(Choice F) Heme consists of an iron bound to protoporphyrin IX. CO binds to iron in metalloproteins but does not cause oxidation of the porphyrin component.

Educational objective:
Carbon monoxide binds heme iron in hemoglobin with an affinity much greater than oxygen, generating carboxyhemoglobin. Remaining binding sites on carboxyhemoglobin have an increased affinity for oxygen that causes the oxygen dissociation curve to shift to the left, impeding oxygen

myoglobin with high affinity, disrupting the heart's ability to use oxygen and thereby decreasing cardiac output. At a cellular level, CO binds to cytochrome oxidase, inhibiting aerobic metabolism and exacerbating tissue hypoxia.

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Carbon monoxide binds heme iron in hemoglobin with an affinity much greater than oxygen, generating carboxyhemoglobin. Remaining binding sites on carboxyhemoglobin have an increased affinity for oxygen that causes the oxygen dissociation curve to shift to the left, impeding oxygen delivery to tissues.

References

- Carbon monoxide intoxication.

Biochemistry	Hematology & Oncology	Carbon monoxide poisoning
Subject	System	Topic

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A 78-year-old man comes to the office due to a one-month history of progressive dyspnea, generalized weakness, fatigue, and palpitations. He also reports tingling and numbness in both lower limbs. His daughter, who is visiting from another state, adds that since his wife's death a year ago, the patient has not been taking care of himself. Blood pressure is 105/50 mm Hg and pulse is 104/min. Cardiovascular examination shows a displaced apical impulse at the sixth intercostal space, a third heart sound, and high-volume, collapsing carotid pulses. Bilateral basal crackles, 2+ bilateral pedal edema, and mild hepatomegaly are also present. Neurologic examination shows decreased light touch and vibration sense in the feet, with decreased knee and ankle reflexes bilaterally. Laboratory evaluation shows normal blood counts. Deficiency of which of the following nutrients is most likely responsible for this patient's symptoms?

A. Ascorbic acid
B. Cobalamin
C. Niacin
D. Pyridoxine
E. Retinol
F. Riboflavin
G. Thiamine

Submit

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- A. Ascorbic acid (1%)
- B. Cobalamin (35%)
- C. Niacin (3%)
- D. Pyridoxine (11%)
- E. Retinol (0%)
- F. Riboflavin (1%)
- ✓ G. Thiamine (45%)

Omitted
Correct answer
G

45%
Answered correctly

01 sec
Time Spent

01/28/2020
Last Updated

Explanation

Water-soluble vitamins

Vitamin	Primary function	Deficiency
B_1 (thiamine)	Decarboxylation of α-keto acids (carbohydrate metabolism)	• Beriberi (peripheral neuropathy, heart failure) • Wernicke-Korsakoff syndrome
B_2 (riboflavin)	Mitochondrial electron carrier (FMN, FAD)	• Angular cheilosis, stomatitis, glossitis • Normocytic anemia
B_3 (niacin)	Electron transfer reactions (NAD/NADP)	• Pellagra (dermatitis, dementia, diarrhea) • Peripheral neuropathy
B_6 (pyridoxine)	Transamination of amino acids (amino acid synthesis)	• Cheilosis, stomatitis, glossitis
B_9 (folate, folic acid)	Hydroxymethyl/formyl carrier (purine & thymine synthesis)	• Megaloblastic anemia • Neural tube defects (fetus)
	Isomerase &	

B_6 (pyridoxine)	Transamination of amino acids (amino acid synthesis)	• Cheilosis, stomatitis, glossitis
B_9 (folate, folic acid)	Hydroxymethyl/formyl carrier (purine & thymine synthesis)	• Megaloblastic anemia • Neural tube defects (fetus)
B_{12} (cobalamin)	Isomerase & methyltransferase cofactor (DNA & methionine synthesis)	• Megaloblastic anemia • Neurologic deficits
C (ascorbic acid)	Hydroxylation of proline & lysine (collagen synthesis)	• Scurvy

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Thiamine deficiency causes infantile and adult beriberi as well as **Wernicke-Korsakoff syndrome** (confusion, ataxia, oculomotor abnormalities, and permanent memory deficits). Manifestations of infantile beriberi appear at age 2-3 months and include a fulminant cardiac syndrome with cardiomegaly, tachycardia, cyanosis, dyspnea, and vomiting. Adult **beriberi** is categorized as dry or wet depending on cardiac involvement. Dry beriberi is characterized by symmetrical **peripheral neuropathy** of the distal extremities, with resulting sensory and motor impairments. Wet beriberi includes the addition of **cardiac involvement** (cardiomyopathy, high-output congestive heart failure, peripheral edema, and tachycardia). Central nervous system involvement (ie, Wernicke-Korsakoff syndrome) occurs primarily in alcoholics.

(Choice A) Ascorbic acid (vitamin C) deficiency causes scurvy (petechial hemorrhages, gingival swelling, impaired wound healing, and weakened immune response).

(Choice B) Vitamin B_{12} (cobalamin) deficiency typically presents as macrocytic anemia. Neurologic involvement can cause upper and lower

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(Choice B) Vitamin B_{12} (cobalamin) deficiency typically presents as macrocytic anemia. Neurologic involvement can cause upper and lower motor neuron dysfunction and sensory peripheral neuropathy.

(Choice C) Niacin deficiency causes pellagra (dementia, dermatitis, and diarrhea).

(Choice D) Pyridoxine (vitamin B_6) deficiency is characterized by cheilosis, glossitis, dermatitis, and affective symptoms.

(Choice E) Vitamin A (retinol) deficiency is characterized by night blindness, xerophthalmia, and vulnerability to infection (especially measles).

(Choice F) Common manifestations of vitamin B_2 (riboflavin) deficiency include cheilosis, stomatitis, glossitis, anemia, and seborrheic dermatitis.

Educational objective:
Thiamine deficiency causes beriberi and Wernicke-Korsakoff syndrome. Dry beriberi is characterized by symmetrical peripheral neuropathy; wet beriberi includes the addition of high-output congestive heart failure.

Biochemistry	Cardiovascular System	Dilated cardiomyopathy
Subject	System	Topic

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A microbiologist performs a genetic experiment in which cultures of *Escherichia coli* are treated with a chemical that induces a high frequency of mutations. Individual bacterial colonies are isolated to identify a mutant strain that lacks a specific enzyme involved in DNA replication. This specific enzyme is responsible for removing short fragments of RNA that are base paired to the DNA template. Which of the following enzymes is most likely deficient in this strain of *E coli*?

- A. DNA polymerase I
- B. DNA polymerase III
- C. Gyrase
- D. Helicase
- E. Ligase
- F. Primase

Submit

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- ✓ A. DNA polymerase I (55%)
- B. DNA polymerase III (17%)
- C. Gyrase (3%)
- D. Helicase (1%)
- E. Ligase (8%)
- F. Primase (13%)

Omitted
Correct answer
A

55%
Answered correctly

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01/20/2020
Last Updated

Explanation

Prokaryotic DNA replication fork

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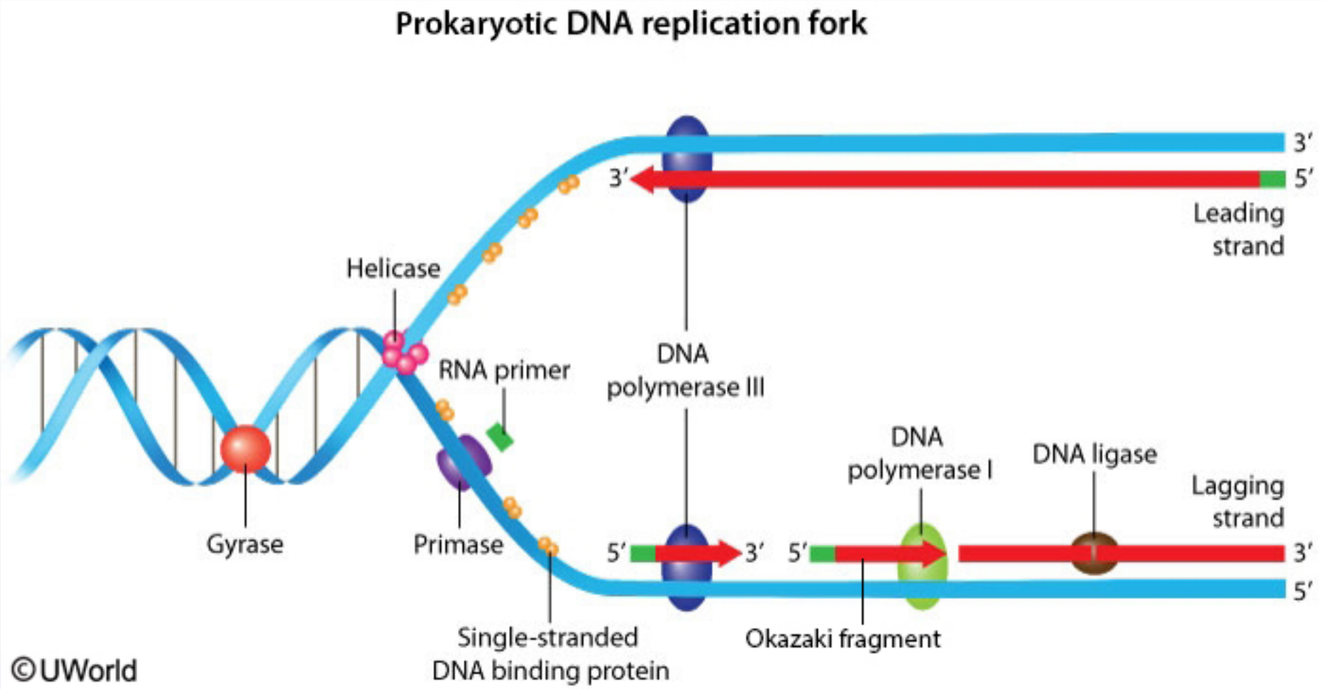

Bacterial DNA replication is coordinated by the actions of multiple enzymes and proteins. Before DNA synthesis begins, helicase binds double-stranded DNA at the origin of replication with the assistance of DnaA protein and acts at the replication fork to unwind and separate the DNA **(Choice D)**. Single-stranded DNA-binding protein then attaches to the separated strands to prevent their reannealing. Unwinding and separation of DNA produces positive supercoils that can lead to DNA fracture if not relieved. Topoisomerase II (DNA gyrase) relieves the tension created during unwinding by introducing negative supercoils into the DNA **(Choice C)**.

Before DNA polymerase III can begin elongating a new DNA strand, it requires an RNA primer made up of short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase) **(Choice F)**. DNA synthesis then proceeds in the 5' to 3' direction with the leading strand being formed continuously toward the replication fork and the lagging strand being formed discontinuously away from the replication fork. Replication of the lagging strand results in the formation of numerous short DNA segments called Okazaki fragments. These fragments are ultimately bound together by the enzyme ligase after their RNA primers have been removed and

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DNA binding protein

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The **removal of RNA primers** and their replacement with DNA is accomplished by **DNA polymerase I**, the only bacterial DNA polymerase with **5' to 3' exonuclease activity**. DNA polymerase III has 5' to 3' polymerase and 3' to 5' exonuclease ("proofreading") activity; however, it cannot remove RNA primers as it lacks 5' to 3' exonuclease activity **(Choice B)**.

Educational objective:
During bacterial DNA replication, DNA polymerase I functions to remove RNA primers (via 5' to 3' exonuclease activity) and replace them with DNA (via 5' to 3' polymerase activity). DNA polymerase I is the only bacterial DNA polymerase that possesses 5' to 3' exonuclease activity.

References

- DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.

Biochemistry	Infectious Diseases	Escherichia coli
Subject	System	Topic

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Erythroblasts isolated from a bone marrow biopsy sample of a patient with neonatal jaundice are incubated in a medium containing radiolabeled glucose. The cells are unable to generate NADPH from glucose metabolism but are able to convert fructose-6-phosphate to ribose-5-phosphate, which is required for nucleic acid synthesis. Which of the following enzymes is essential for the latter conversion?

A. Aconitase

B. Enolase

C. Glucose-6-phosphate dehydrogenase

D. Glutathione reductase

E. Transketolase

Submit

Erythroblasts isolated from a bone marrow biopsy sample of a patient with neonatal jaundice are incubated in a medium containing radiolabeled glucose. The cells are unable to generate NADPH from glucose metabolism but are able to convert fructose-6-phosphate to ribose-5-phosphate, which is required for nucleic acid synthesis. Which of the following enzymes is essential for the latter conversion?

- A. Aconitase (3%)
- B. Enolase (11%)
- C. Glucose-6-phosphate dehydrogenase (18%)
- D. Glutathione reductase (7%)
- ✓ E. Transketolase (59%)

Omitted
Correct answer
E

59%
Answered correctly

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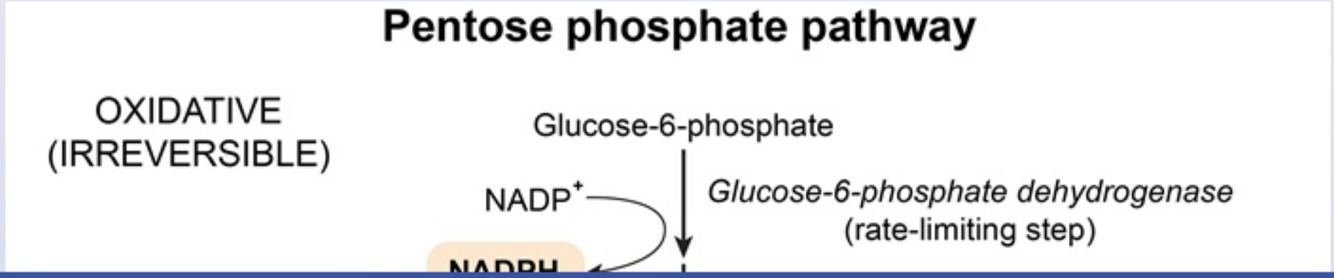
Time Spent

05/11/2020
Last Updated

Explanation



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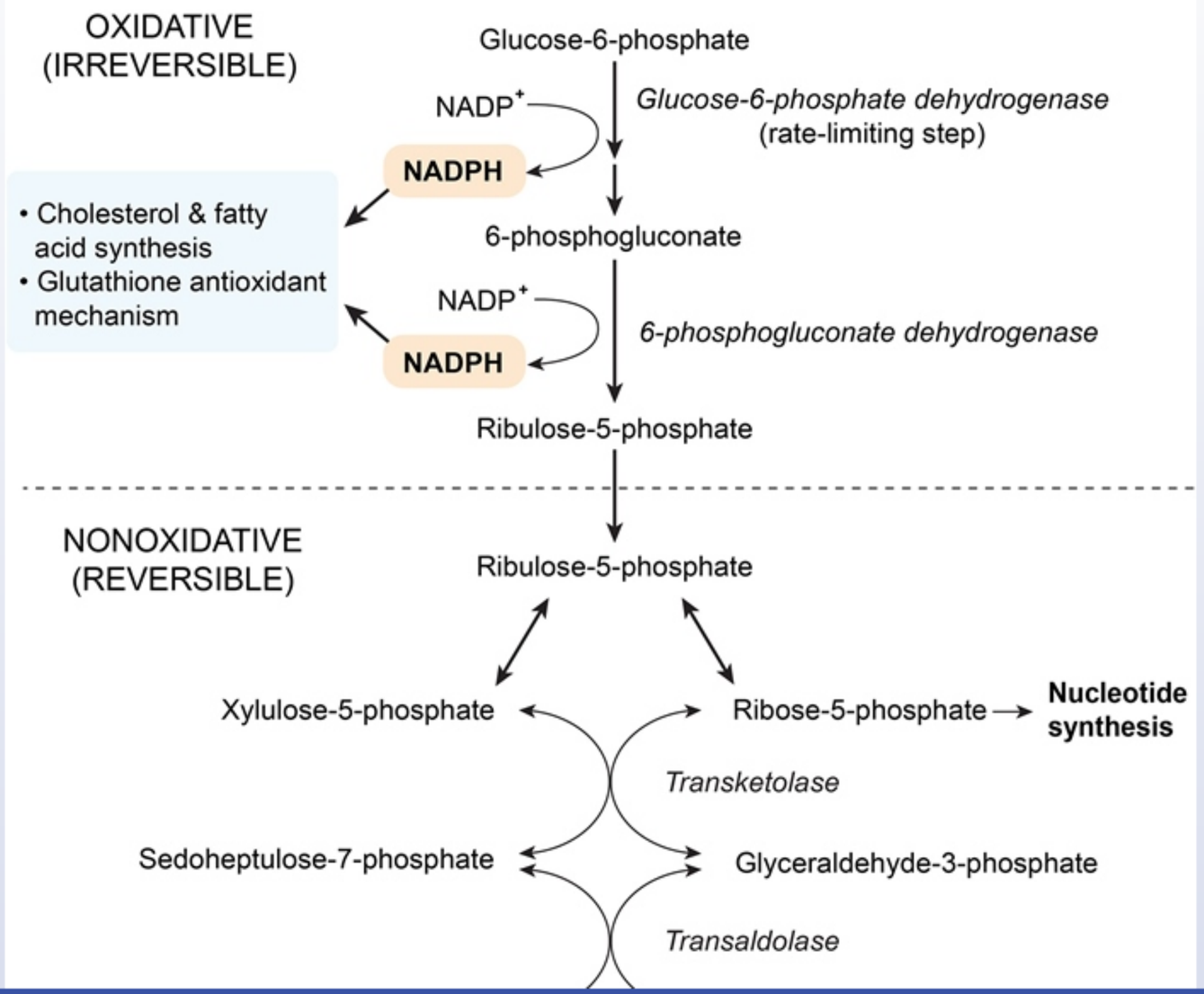
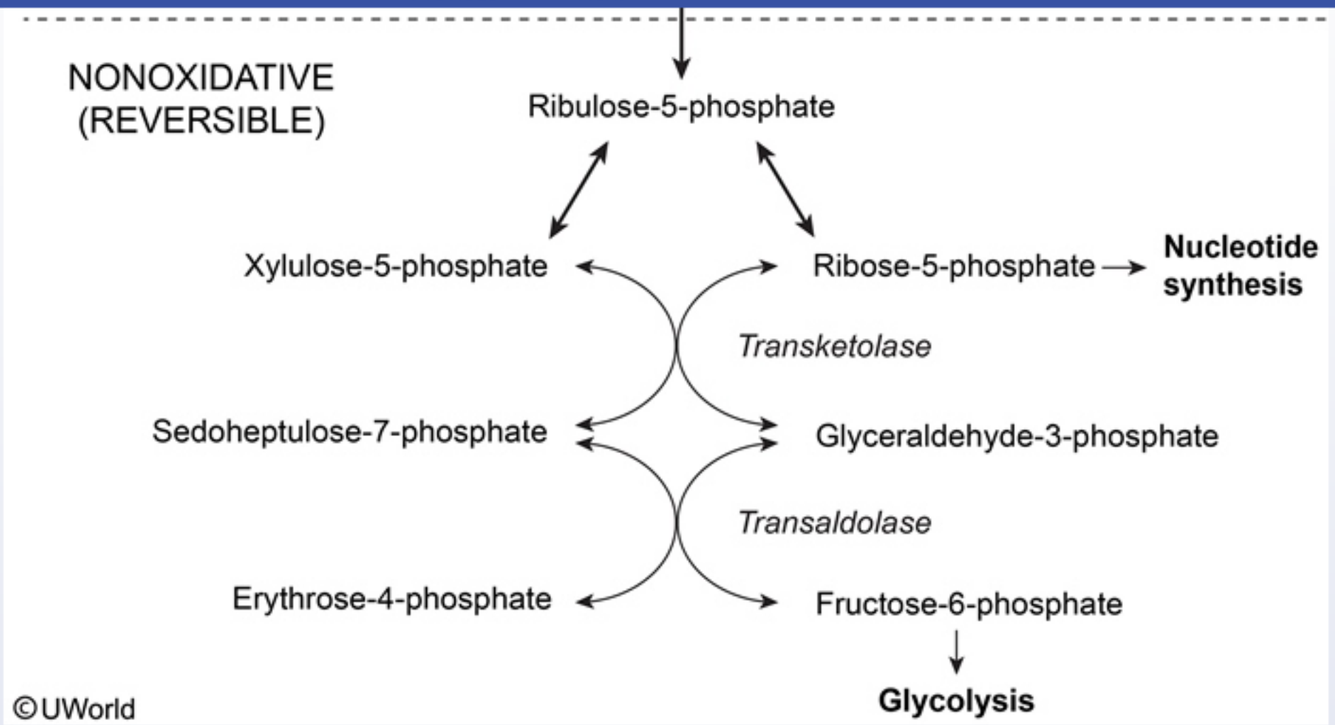
Pentose phosphate pathway





The **pentose phosphate pathway** (HMP shunt) generates **NADPH** for use in reductive reactions and **ribose-5-phosphate**, a precursor for the synthesis of nucleotides. The pathway consists of 2 types of reactions, oxidative (irreversible) and nonoxidative (reversible), both of which can function independently depending on cellular requirements.

Activity of the nonoxidative reactions is governed by the cellular demand for ribose-5-phosphate. When ribose-5-phosphate is produced in excess, transketolase and transaldolase can produce the **glycolytic intermediates** glyceraldehyde-3-phosphate and fructose-6-phosphate for ATP generation. When ribose-5-phosphate demand exceeds the production capabilities of the oxidative pathway, the nonoxidative pathway functions in **reverse** and transketolase and transaldolase catalyze the conversion of fructose-6-phosphate and glycerldehyde-3-phosphate to ribose-5-phosphate.

(Choice A) Aconitase catalyzes the isomerization of citrate to isocitrate in the citric acid cycle.

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Glycolysis

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(Choice A) Aconitase catalyzes the isomerization of citrate to isocitrate in the citric acid cycle.

(Choice B) Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate in glycolysis.

(Choice C) Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway. Deficiency of this enzyme results in hemolytic anemia due to the inability to generate NADPH in the oxidative portion of the pathway. However, nonoxidative reactions are responsible for conversion of fructose-6-phosphate to ribose-5-phosphate.

(Choice D) Glutathione reductase catalyzes the reduction of glutathione disulfide to glutathione using NADPH. Glutathione aids red blood cells in resisting oxidative stress.

Educational objective:
The pentose phosphate pathway consists of an oxidative (irreversible) branch and a nonoxidative (reversible) branch, and each can function independently based on cellular requirements. Transketolase, an enzyme of the nonoxidative branch, is responsible in part for the interconversion of ribose-5-phosphate (nucleotide precursor) and fructose-6-phosphate (glycolytic intermediate).

References

- The pentose phosphate pathway and cancer.

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References

- The pentose phosphate pathway and cancer.

Biochemistry	Hematology & Oncology	G6PD deficiency
Subject	System	Topic

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A 42-year-old man comes to the office due to numbness and tingling in both legs and difficulty walking for the past several months. He has also noticed that he tires more easily with physical activity. His temperature is 36.8 C (98 F), blood pressure is 122/86 mm Hg, pulse is 76 /min, and respirations are 14/min. Physical examination shows conjunctival pallor and loss of vibration and position sensation in the bilateral lower extremities with associated gait ataxia. The remainder of the examination is within normal limits. Which of the following findings is most likely to be present upon further questioning of the patient?

A. Ongoing treatment for latent tuberculosis

B. Strict vegan diet for the past 6 years

C. Total gastrectomy 8 months ago

D. Use of an anti-epileptic drug for the past 3 months

E. Working indoors most of the time

Submit

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- A. Ongoing treatment for latent tuberculosis (5%)
- ✓ B. Strict vegan diet for the past 6 years (65%)
- C. Total gastrectomy 8 months ago (26%)
- D. Use of an anti-epileptic drug for the past 3 months (2%)
- E. Working indoors most of the time (0%)

Omitted
Correct answer
B

65%
Answered correctly

02 secs
Time Spent

01/21/2020
Last Updated

Explanation

Vitamin B_{12} deficiency

Methylmalonic acid **Buildup** **Impaired**

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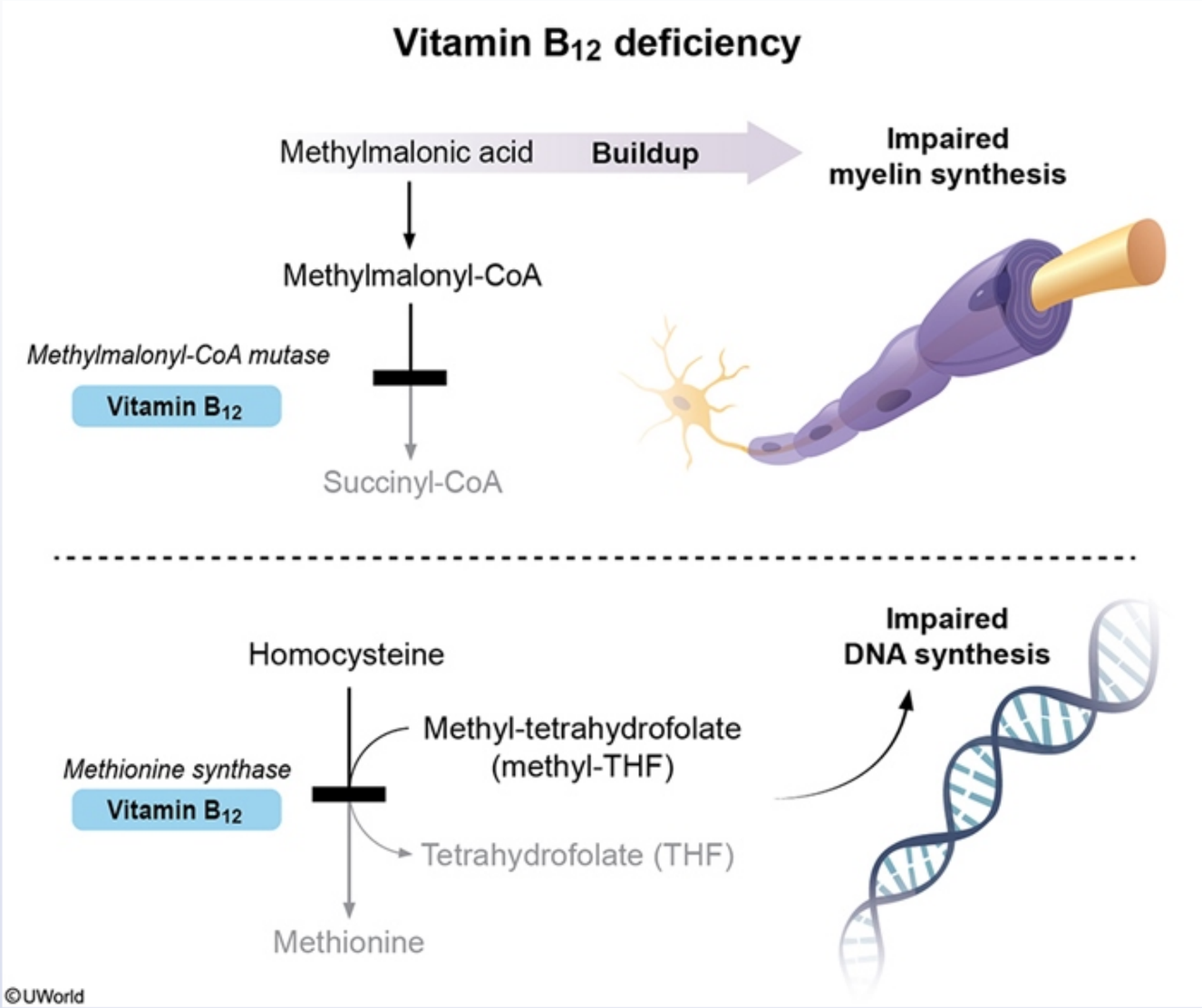

Vitamin B12 (cobalamin) is obtained solely from the diet, specifically from **animal products** such as meat, dairy, and fish. Vitamin B_{12} cannot be

Vitamin B12 (cobalamin) is obtained solely from the diet, specifically from **animal products** such as meat, dairy, and fish. Vitamin B_{12} cannot be obtained from plant products, placing **strict vegans at risk for dietary deficiency**. The body is capable of storing about 1,000 times the daily requirement; therefore, vitamin B_{12} deficiency develops only after the **complete absence of intake for 4-5 years**.

The development of **anemia** as well as severe and potentially irreversible neurologic damage can result from vitamin B_{12} deficiency. Red blood cell synthesis relies on vitamin B_{12}-dependent recycling of folate; deficiency of either vitamin results in a megaloblastic anemia. Neurologic symptoms vary in severity, but patients typically present with both motor and sensory deficits. Impaired myelin synthesis, specifically in the dorsal and lateral columns, results in **subacute combined degeneration of the spinal cord**. This condition is progressive and begins as a symmetrical neuropathy consisting of paresthesias and weakness. Ongoing deficiency leads to loss of vibration and position sensation with development of an ataxic gait. The longer the deficiency is untreated, the less likely it can be reversed.

(Choice A) Isoniazid, one of several drugs used to treat tuberculosis, may result in vitamin B_6 deficiency. Clinical manifestations consist of stomatitis, cheilosis, atrophic glossitis, sideroblastic anemia, and peripheral neuropathy. However, this patient's lack of oropharyngeal findings makes vitamin B_6 deficiency less likely.

(Choice C) Patients undergoing total gastrectomy will inevitably develop B_{12} deficiency if not given vitamin supplementation. However, this deficiency takes years to develop due to the large hepatic B_{12} reserve, and would not occur after a period of only 8 months.

(Choice D) Phenytoin, an anti-epileptic drug used to treat both focal and generalized seizures, may result in folate deficiency and development of megaloblastic anemia. Phenytoin can also cause peripheral neuropathy, but this side effect usually only occurs with chronic therapy (>1 year).

(Choice E) Vitamin D deficiency can develop over the course of several months due to inadequate dietary intake and minimal sunlight exposure. This deficiency presents as rickets in children and osteomalacia or osteoporosis in adults.

Educational objective:
Vitamin B_{12} is obtained through the diet solely from animal sources, which places strict vegans at risk for dietary deficiency. This deficiency takes years to develop due to the large hepatic B_{12} reserve, and presents with megaloblastic anemia and potentially irreversible neurologic deficits (eg, paresthesias, weakness, ataxic gait).

Biochemistry Hematology & Oncology Vitamin b12 deficiency

The development of **anemia** as well as severe and potentially irreversible neurologic damage can result from vitamin B_{12} deficiency. Red blood cell synthesis relies on vitamin B_{12}-dependent recycling of folate; deficiency of either vitamin results in a megaloblastic anemia. Neurologic symptoms vary in severity, but patients typically present with both motor and sensory deficits. Impaired myelin synthesis, specifically in the dorsal and lateral columns, results in **subacute combined degeneration of the spinal cord**. This condition is progressive and begins as a symmetrical neuropathy consisting of paresthesias and weakness. Ongoing deficiency leads to loss of vibration and position sensation with development of an ataxic gait. The longer the deficiency is untreated, the less likely it can be reversed.

(Choice A) Isoniazid, one of several drugs used to treat tuberculosis, may result in vitamin B_6 deficiency. Clinical manifestations consist of stomatitis, cheilosis, atrophic glossitis, sideroblastic anemia, and peripheral neuropathy. However, this patient's lack of oropharyngeal findings makes vitamin B_6 deficiency less likely.

(Choice C) Patients undergoing total gastrectomy will inevitably develop B_{12} deficiency if not given vitamin supplementation. However, this deficiency takes years to develop due to the large hepatic B_{12} reserve, and would not occur after a period of only 8 months.

(Choice D) Phenytoin, an anti-epileptic drug used to treat both focal and generalized seizures, may result in folate deficiency and development of megaloblastic anemia. Phenytoin can also cause peripheral neuropathy, but this side effect usually only occurs with chronic therapy (>1 year).

(Choice E) Vitamin D deficiency can develop over the course of several months due to inadequate dietary intake and minimal sunlight exposure. This deficiency presents as rickets in children and osteomalacia or osteoporosis in adults.

Educational objective:
Vitamin B_{12} is obtained through the diet solely from animal sources, which places strict vegans at risk for dietary deficiency. This deficiency takes years to develop due to the large hepatic B_{12} reserve, and presents with megaloblastic anemia and potentially irreversible neurologic deficits (eg, paresthesias, weakness, ataxic gait).

Biochemistry	Hematology & Oncology	Vitamin b12 deficiency
Subject	System	Topic

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A 6-year-old African American boy is brought to the physician because of easy fatigability. Physical examination reveals splenomegaly, and his complete blood count shows mild anemia. Hemoglobin electrophoresis is performed at alkaline pH on a cellulose acetate strip. Findings for the patient are shown below compared to individuals with normal hemoglobin and known sickle cell disease.

Which of the following is the most likely cause of this patient's condition?

A. Alpha globin gene deletion
B. Missense mutation
C. Nonsense mutation
D. Silent mutation
E. Trinucleotide expansion

Submit

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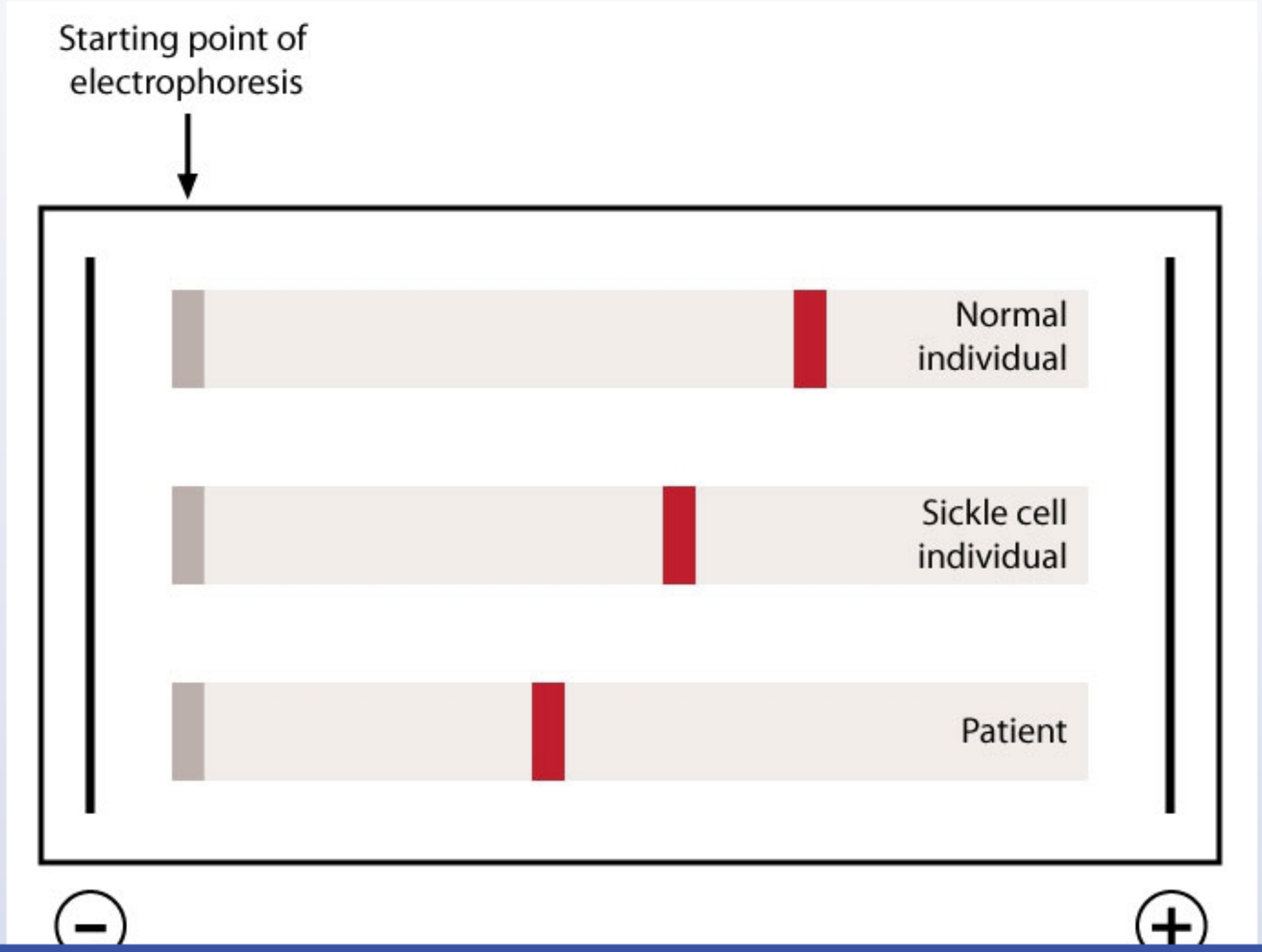

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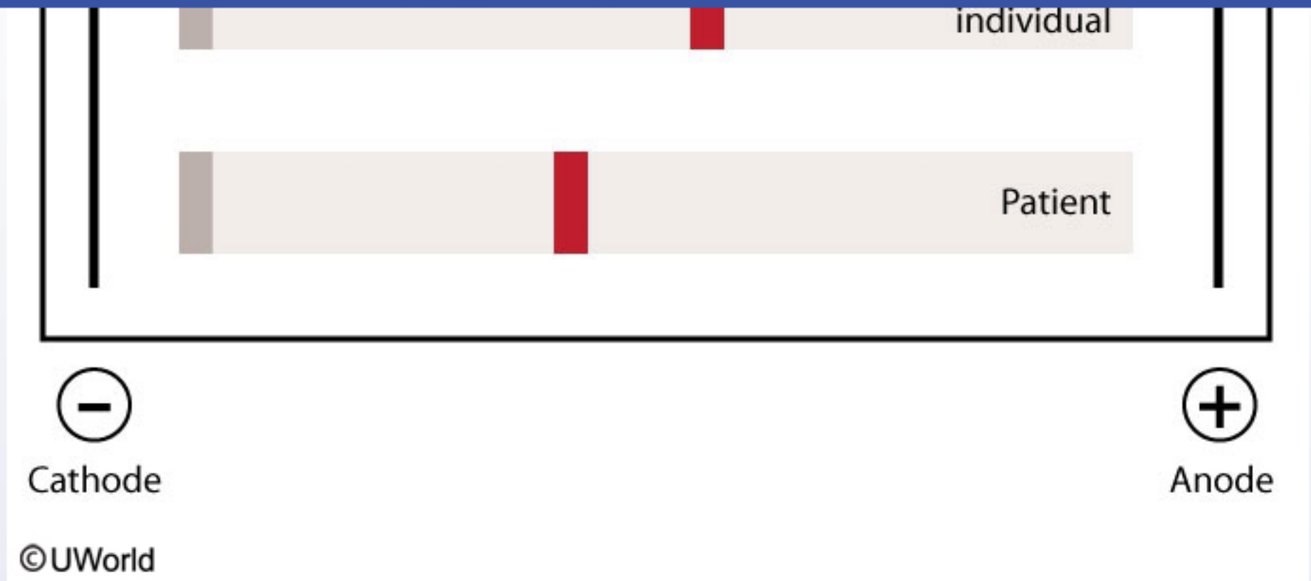

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- A. Alpha globin gene deletion
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- C. Nonsense mutation
- D. Silent mutation
- E. Trinucleotide expansion

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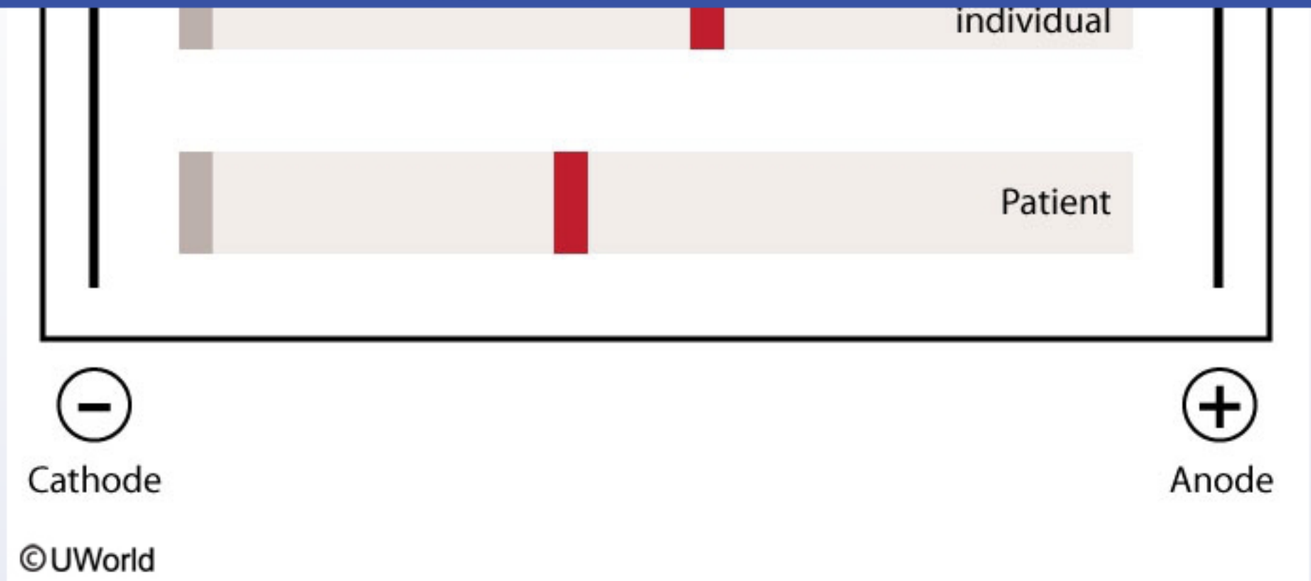

Which of the following is the most likely cause of this patient's condition?

- A. Alpha globin gene deletion (23%)
- ✓ B. Missense mutation (55%)
- C. Nonsense mutation (14%)
- D. Silent mutation (0%)
- E. Trinucleotide expansion (6%)

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Correct answer

55%
Answered correctly

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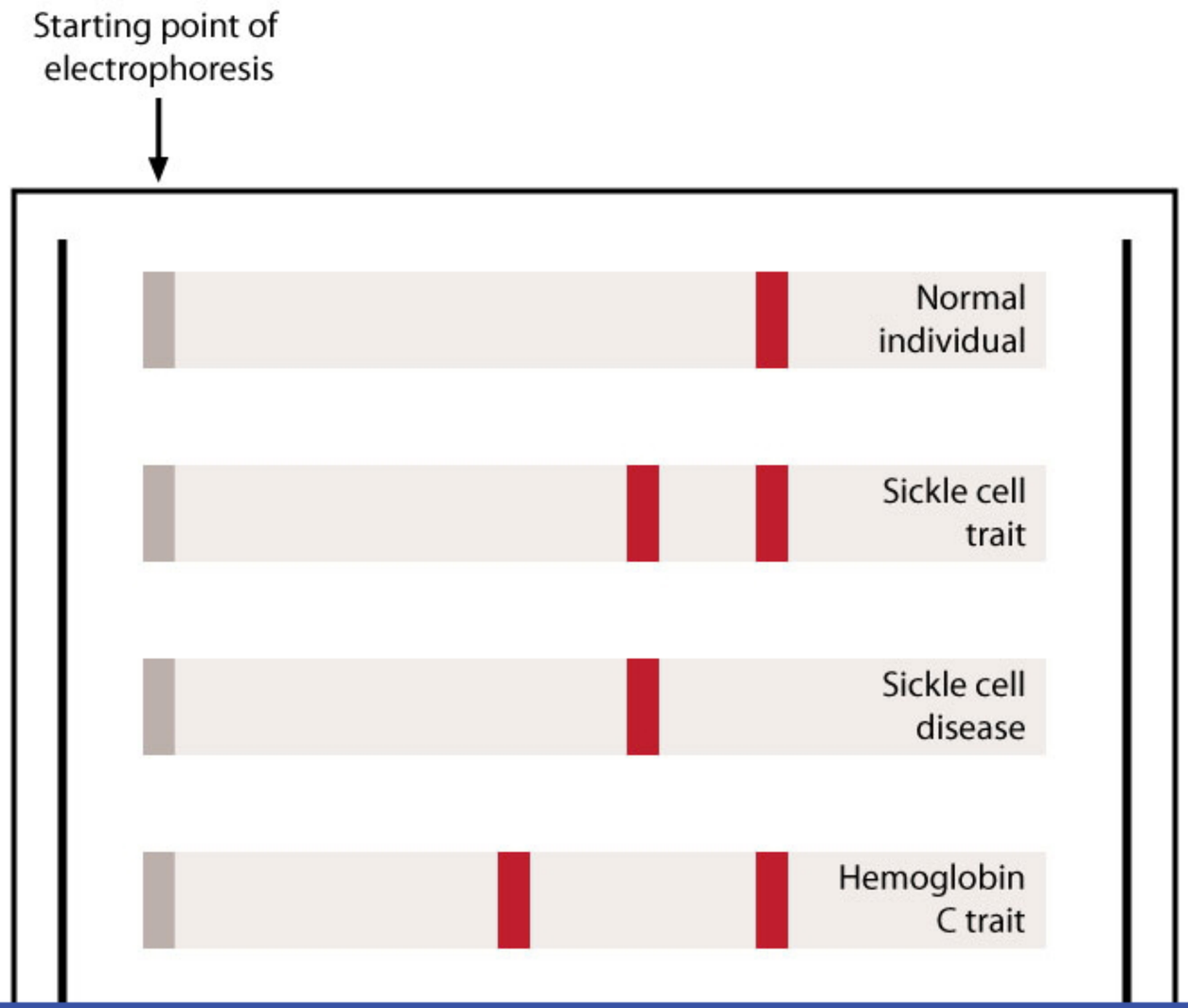
03/04/2020
Last Updated

Hemoglobinopathy electrophoresis patterns



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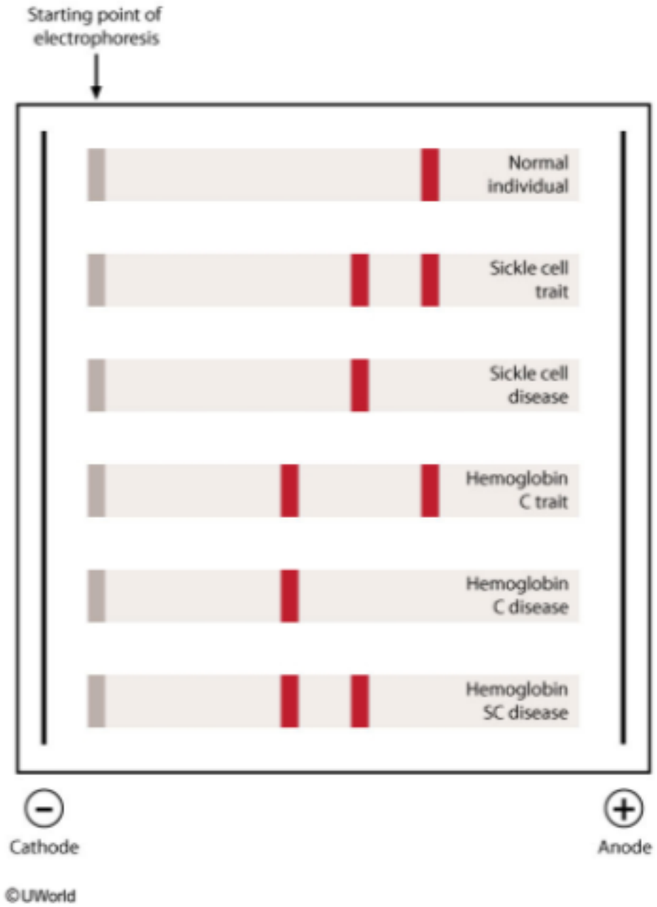
Hemoglobinopathy electrophoresis patterns



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Hemoglobin electrophoresis is used to assess for different forms of hemoglobin in patients with suspected hemoglobinopathy. Normal hemoglobin consists primarily of **hemoglobin A** (HbA), which **migrates rapidly** toward the positive electrode (anode) because of its negative charge. Hemoglobin S (HbS) is an abnormal type of hemoglobin in which a nonpolar amino acid (valine) replaces a negatively charged amino acid (glutamate) in the beta globin chain. This amino acid replacement decreases the negative charge on the HbS molecule, which causes **HbS** to move more **slowly** toward the anode. Similarly, hemoglobin C (HbC) has a glutamate residue replaced by lysine in the beta globin chain. Because lysine is a positively charged amino acid, **HbC** has even less total negative charge than HbS and moves **even more slowly** toward the anode. Both HbC and HbS result from **missense mutations**, a type of mutation in which a single base substitution results in a codon that codes for a different amino acid.

Patients with sickle cell disease have HbS mutations in both beta chains; those with HbC disease have HbC mutations involving both beta chains. Patients with hemoglobin SC disease have 1 HbS allele and 1 HbC allele and will have 2 hemoglobin bands on electrophoresis. This patient's electrophoresis results show a **single band** that **migrates less than the HbA and HbS** bands, meaning that he has **HbC disease**. Patients with HbC disease are typically asymptomatic and often have mild hemolytic anemia and splenomegaly.

(Choice A) Deletions involving the alpha globin genes cause alpha thalassemia, which results in imbalanced beta chain production and formation of beta tetramers (hemoglobin H) that migrate further than HbA during electrophoresis.

(Choice C) Nonsense mutations introduce a stop codon within gene sequences, resulting in the formation of truncated proteins. As a result of their decreased size, these proteins tend to move further during electrophoresis.

(Choice D) Silent mutations are point mutations that have no effect on the protein formed. A mutation from UCA to UCC does not result in any change in protein structure as both codons result in the placement of serine into the growing polypeptide chain.

(Choice E) Trinucleotide expansions increase the number of trinucleotide repeats within a gene, resulting in large, unstable proteins or alterations in the epigenetic effects. These proteins would tend to move less during electrophoresis due to their increased size. However, the hemoglobinopathies are not caused by trinucleotide expansions, as the hemoglobin genes do not contain trinucleotide repeat regions.

Educational objective:
Hemoglobin C is caused by a missense mutation that results in a glutamate residue being substituted by lysine in the beta globin chain. This results in an overall decrease in negative charge for the hemoglobin molecule. The speed of hemoglobin movement during gel electrophoresis is

anode. Both HbC and HbS result from **missense mutations**, a type of mutation in which a single base substitution results in a codon that codes for a different amino acid.

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Educational objective:
Hemoglobin C is caused by a missense mutation that results in a glutamate residue being substituted by lysine in the beta globin chain. This results in an overall decrease in negative charge for the hemoglobin molecule. The speed of hemoglobin movement during gel electrophoresis is hemoglobin A > hemoglobin S > hemoglobin C.

Biochemistry	Hematology & Oncology	Hemoglobin c disease
Subject	System	Topic

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Hemoglobin

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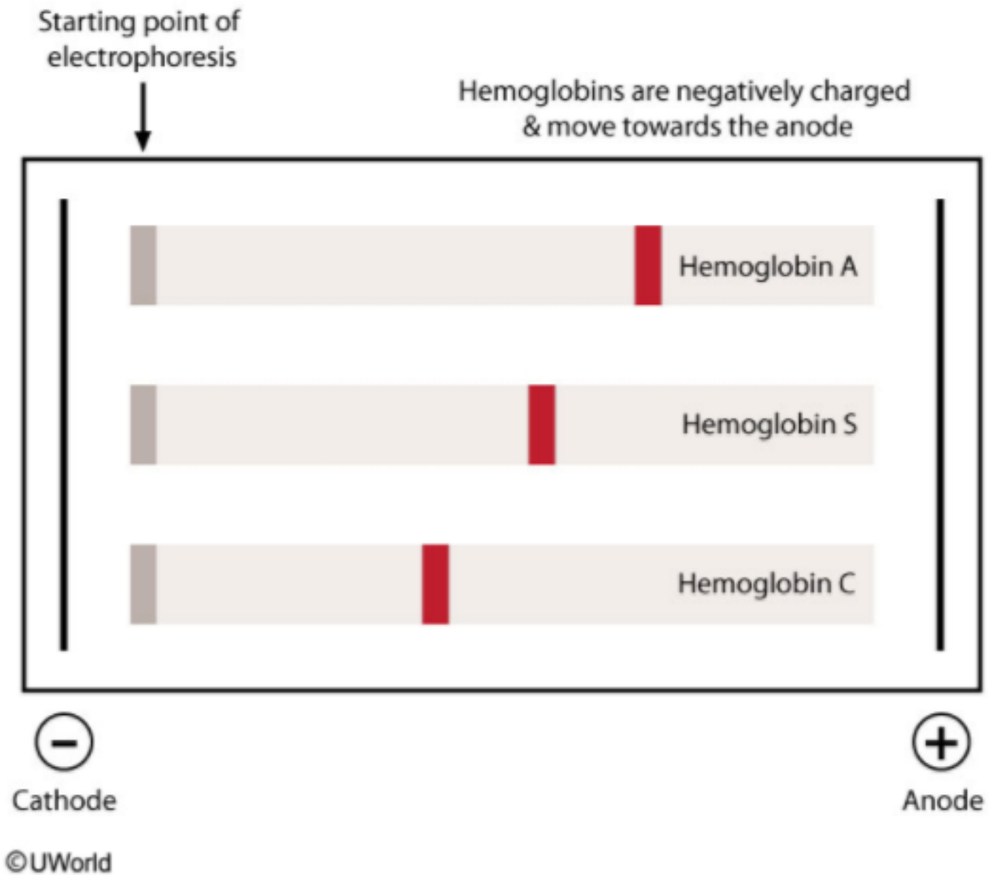
Hemoglobin electrophoresis



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anode. Both HbC and HbS result from **missense mutations**, a type of mutation in which a single base substitution results in a codon that codes

A 13-year-old girl is undergoing hematologic evaluation. She is found to have a hemoglobin mutation that changes the partial pressure of oxygen at which hemoglobin is 50% saturated to 20 mm Hg. In comparison, normal hemoglobin becomes 50% saturated with oxygen at 26 mm Hg. Which of the following sequelae is this patient most likely to develop as a result of her mutation?

- A. Erythrocytosis
- B. Hypoxia-induced hemolysis
- C. Increased erythrocyte osmotic fragility
- D. Megaloblastic erythrocyte changes
- E. Oxidant-induced hemolysis

Submit

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- ✓ A. Erythrocytosis (53%)
- B. Hypoxia-induced hemolysis (20%)
- C. Increased erythrocyte osmotic fragility (7%)
- D. Megaloblastic erythrocyte changes (2%)
- E. Oxidant-induced hemolysis (16%)

Omitted
Correct answer
A

53%
Answered correctly

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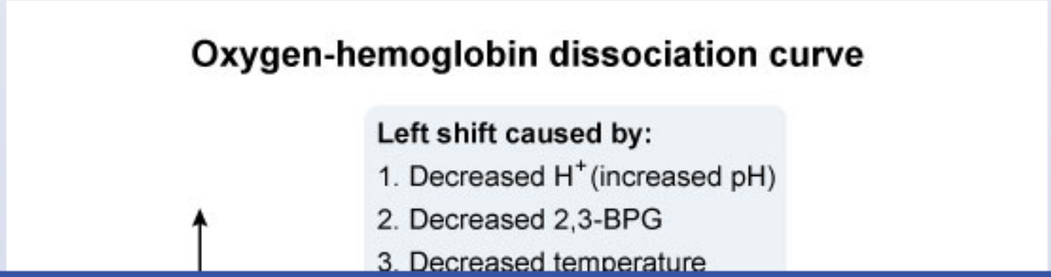
03/03/2020
Last Updated

Explanation



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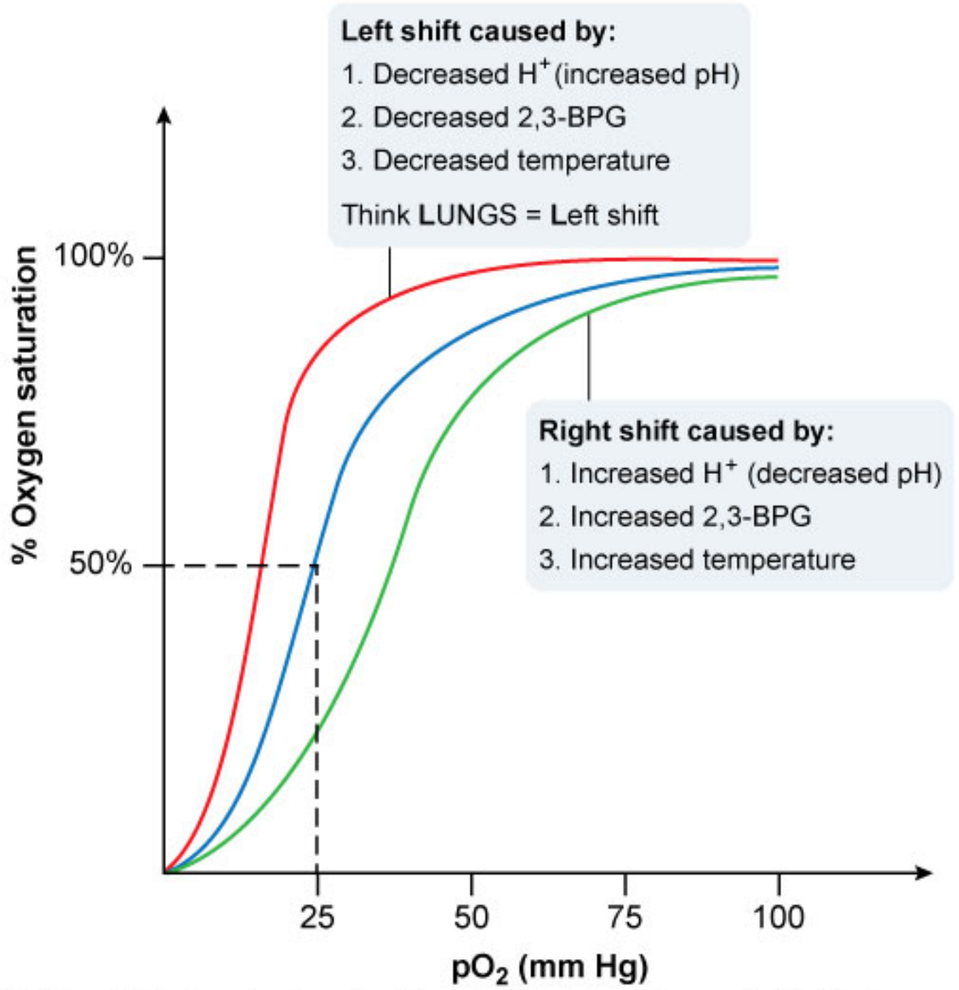
Oxygen-hemoglobin dissociation curve



2,3-BPG = 2,3-bisphosphoglycerate; **pO_2** = partial pressure of oxygen in the blood.

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The **oxygen-hemoglobin dissociation curve** describes the relationship between the partial pressure of oxygen in the blood and the oxygen saturation of hemoglobin. The partial pressure of oxygen at which hemoglobin is 50% saturated (**P_{50}**) is a value used as a conventional measure of hemoglobin's affinity for oxygen. The P_{50} is about 26 mm Hg in normal individuals. A P_{50} **shift from 26 to 20 mm Hg** indicates that the affinity of hemoglobin for oxygen is increased (left shift of the oxygen dissociation curve).

Mutations that cause production of hemoglobin with **high oxygen affinity** (eg, hemoglobins Chesapeake and Kempsey) reduce the ability of hemoglobin to release oxygen within the peripheral tissues. Low oxygen levels stimulate the kidneys to increase erythropoietin synthesis, which results in a **compensatory erythrocytosis** that helps maintain normal oxygen delivery. Therefore, patients with high oxygen affinity hemoglobins are typically asymptomatic.

(Choice B) Sickle cell disease can result in hypoxia-induced hemolysis due to the ability of deoxygenated hemoglobin S to polymerize and cause excessive erythrocyte sickling and irreversible cell membrane damage. The oxygen dissociation curve for hemoglobin S is shifted to the right (↓ oxygen affinity) due to the stabilizing effects of polymerization on the deoxygenated form.

(Choice C) Hereditary spherocytosis results from a variety of molecular defects involving erythrocyte structural proteins responsible for linking the plasma membrane to the cytoskeleton (eg, spectrin, ankyrin). The resulting membrane instability leads to the formation of spherocytes – small, rounded erythrocytes with increased susceptibility to lyse in hypotonic solutions.

(Choice D) Megaloblastic erythrocyte changes (↑ MCV) are characteristically seen in vitamin B_{12} and folic acid deficiency due to impaired DNA synthesis.

(Choice E) Individuals with glucose-6-phosphate dehydrogenase deficiency develop rapid hemolysis during periods of increased oxidant stress, such as when taking antimalarials or sulfonamides or after ingestion of fava beans.

Educational objective:
P_{50} refers to the partial pressure of oxygen at which hemoglobin is 50% saturated. Hemoglobins with high oxygen affinity have a decreased P_{50} that is represented by a leftward shift of the oxygen dissociation curve. The reduced ability to release oxygen within the peripheral tissues leads to renal hypoxia, increased erythropoietin synthesis, and compensatory erythrocytosis.

References

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References

- Hemoglobins with high oxygen affinity leading to erythrocytosis. New variants and new concepts.

Biochemistry	Hematology & Oncology	Hemoglobin properties
Subject	System	Topic

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A 22-year-old man comes to the office due to recurrent blistering on the back of his hands and forearms for the past several years. The patient usually develops small itchy spots but lately has had large blisters that heal with hyperpigmentation after rupturing. He has used over-the-counter topical hydrocortisone and emollients, but the symptoms have not improved. The patient works as a night security guard and has had no exposure to chemicals or animals. He drinks 2-3 cans of beer daily. Physical examination shows vesicles and erosions on the dorsum of both hands. Which of the following enzymes is most likely deficient in this patient?

- A. δ-Aminolevulinate dehydratase
- B. δ-Aminolevulinate synthase
- C. Bilirubin glucuronyl transferase
- D. Porphobilinogen deaminase
- E. Uroporphyrinogen decarboxylase

Submit

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- A. δ-Aminolevulinate dehydratase (7%)
- B. δ-Aminolevulinate synthase (11%)
- C. Bilirubin glucuronyl transferase (4%)
- D. Porphobilinogen deaminase (22%)
- ✓ E. Uroporphyrinogen decarboxylase (53%)

Omitted
Correct answer
E

53%
Answered correctly

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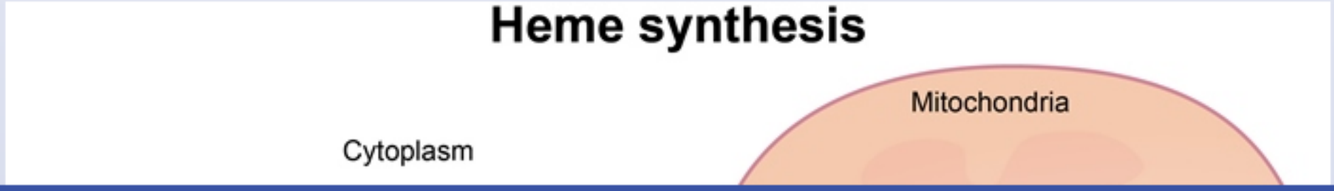
Explanation



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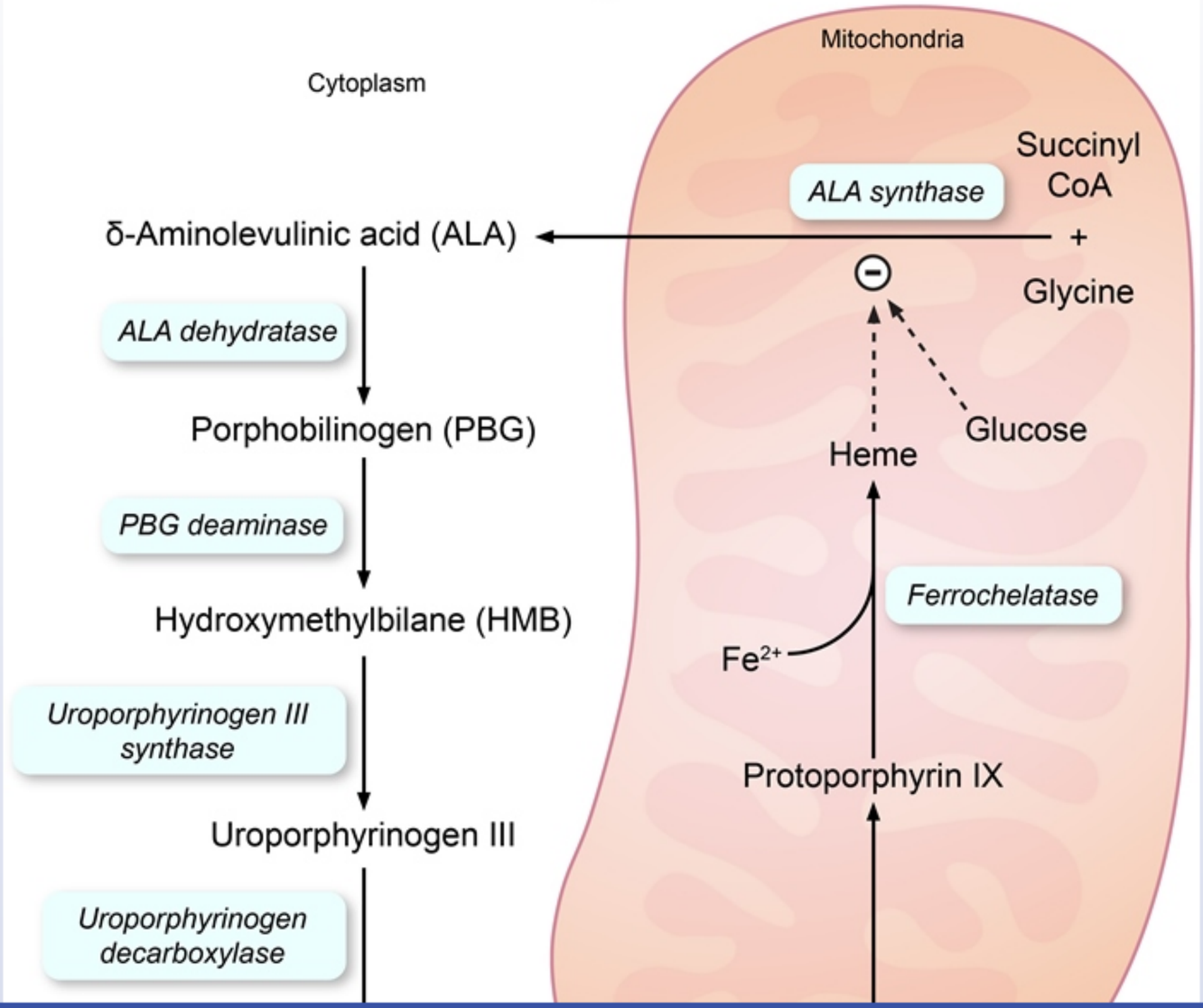
Heme synthesis



Heme synthesis

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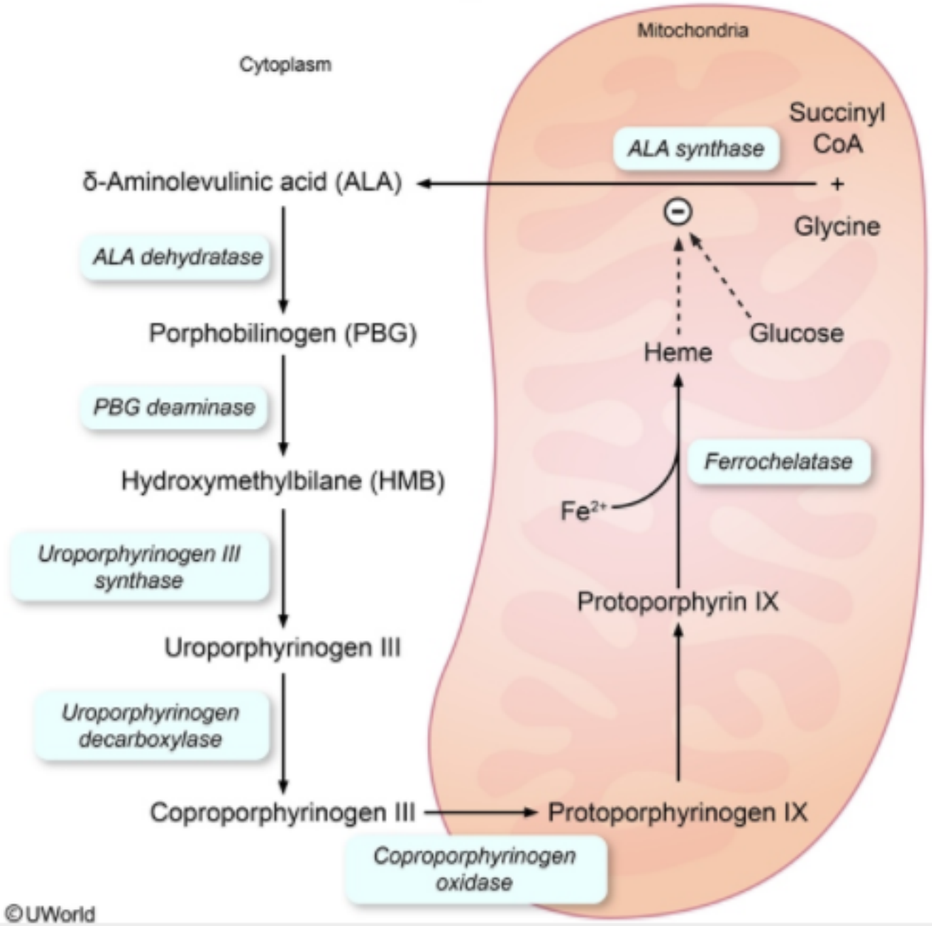
Heme synthesis



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This patient most likely has **porphyria cutanea tarda (PCT)**, the most common disorder of porphyrin (eg, heme) synthesis. Enzyme deficiencies in the early steps in porphyrin synthesis cause abdominal pain and neuropsychiatric manifestations (due to metabolite buildup) without photosensitivity. **Late** step (ie, following porphobilinogen [PBG] conversion) derangements (eg, PCT) cause **photosensitivity**, which is thought to be due to the accumulation of **porphyrinogens** that react with oxygen on excitation by ultraviolet (sun) light.

PCT is caused by **uroporphyrinogen decarboxylase (UROD)** deficiency, which is either inherited or (more commonly) acquired, manifesting in the presence of iron and of susceptibility factors (eg, alcohol [as in this patient], smoking, halogenated hydrocarbons, hepatitis C, HIV). Photosensitivity presents as vesicle and **blister** formation on sun-exposed areas as well as edema, pruritus, pain, and erythema. Deficiencies in coproporphyrinogen oxidase, protoporphyrinogen oxidase, or ferrochelatase can also result in photosensitivity.

(Choices A and D) Deficiencies in aminolevulinate (ALA) dehydratase and PBG deaminase do not result in photosensitivity because the metabolites that accumulate are not porphyrinogens or porphyrins. PBG deaminase deficiency is seen with acute intermittent porphyria (classically presenting with abdominal pain and neuropsychiatric manifestations).

(Choice B) Deficiency of ALA synthase will result in a decrease in formation of all porphyrins. This deficiency will not result in porphyria but will lead to a decrease in heme synthesis and concurrent hypochromic, microcytic anemia. Pyridoxal phosphate (vitamin B_6) is the cofactor required for activity of ALA synthase; therefore, pyridoxine deficiency can result in microcytic hypochromic anemia.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme responsible for the conjugation of bilirubin with glucuronide, improving solubility for biliary excretion. A decrease in glucuronyl transferase results in unconjugated hyperbilirubinemia.

Educational objective:
Enzyme deficiencies of the early steps in porphyrin synthesis cause neuropsychiatric manifestations without photosensitivity, whereas late step derangements lead to photosensitivity. Photosensitivity manifests as vesicle and blister formation on sun-exposed areas as well as edema, pruritus, pain, and erythema.

Biochemistry	Hematology & Oncology	Porphyria cutanea tarda
Subject	System	Topic

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Biochemistry	Hematology & Oncology	Porphyria cutanea tarda
Subject	System	Topic

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A 52-year-old man is being evaluated in the emergency department for abdominal pain associated with watery diarrhea. His symptoms have been progressive over the last month. He says that he is depressed and often has difficulty remembering things. The patient has a 20-year history of alcohol abuse. On examination, he appears disheveled. A pigmented scaly skin rash is present in the malar distribution of his face, neck, and back of his hands. The rash has been present for several months and worsens on exposure to sunlight. It is determined that the patient's symptoms are secondary to lack of a specific nutrient. Activity of which of the following enzymes is most likely decreased in the patient as a result of this deficiency?

A. Citrate synthase

B. Hexokinase

C. Isocitrate dehydrogenase

D. Phosphoglycerate kinase

E. Succinate dehydrogenase

Submit

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- A. Citrate synthase (7%)
- B. Hexokinase (5%)
- ✓ C. Isocitrate dehydrogenase (46%)
- D. Phosphoglycerate kinase (8%)
- E. Succinate dehydrogenase (31%)

Omitted
Correct answer
C

46%
Answered correctly

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Explanation

Niacin dependent enzymes in TCA cycle

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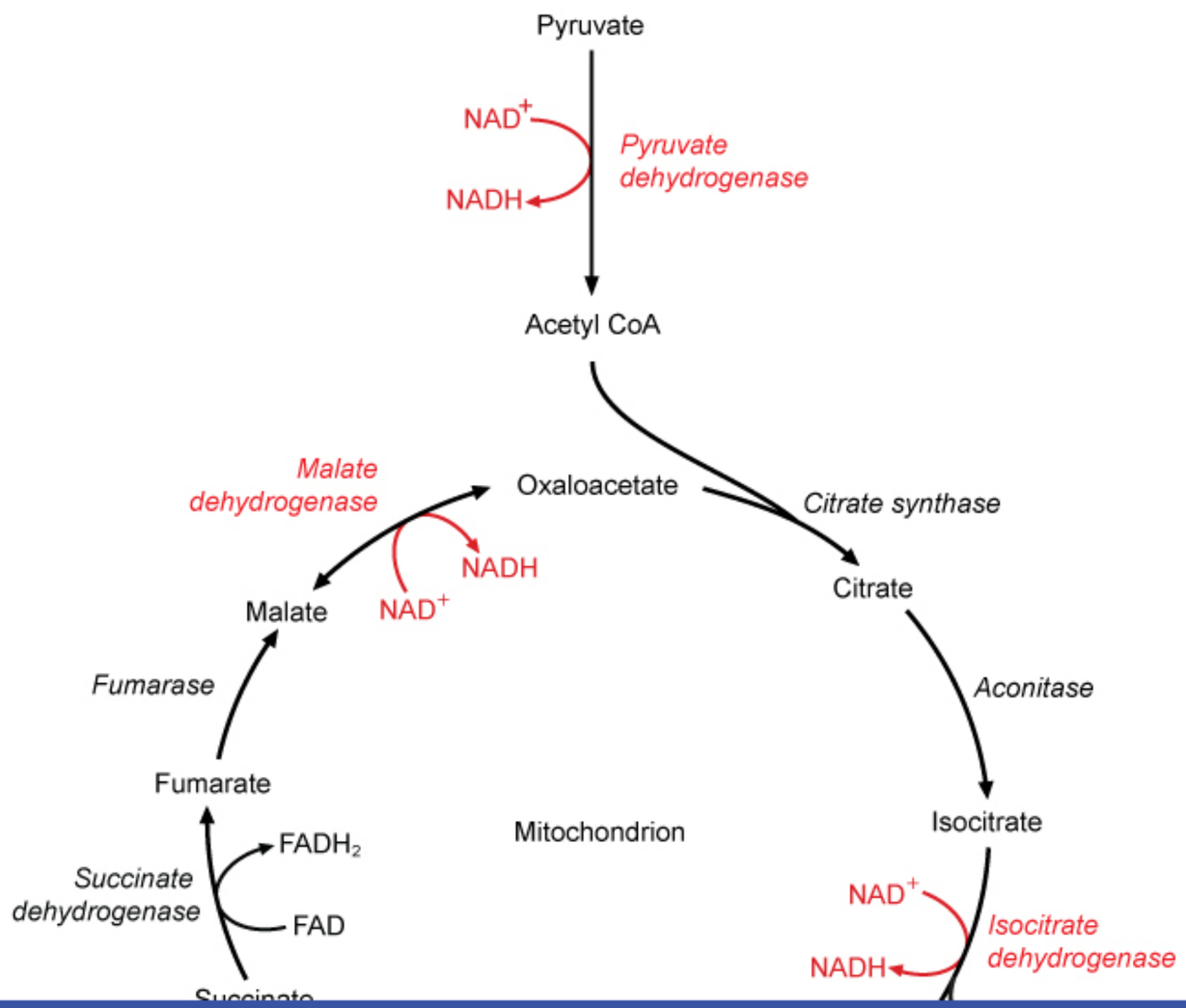
Niacin dependent enzymes in TCA cycle



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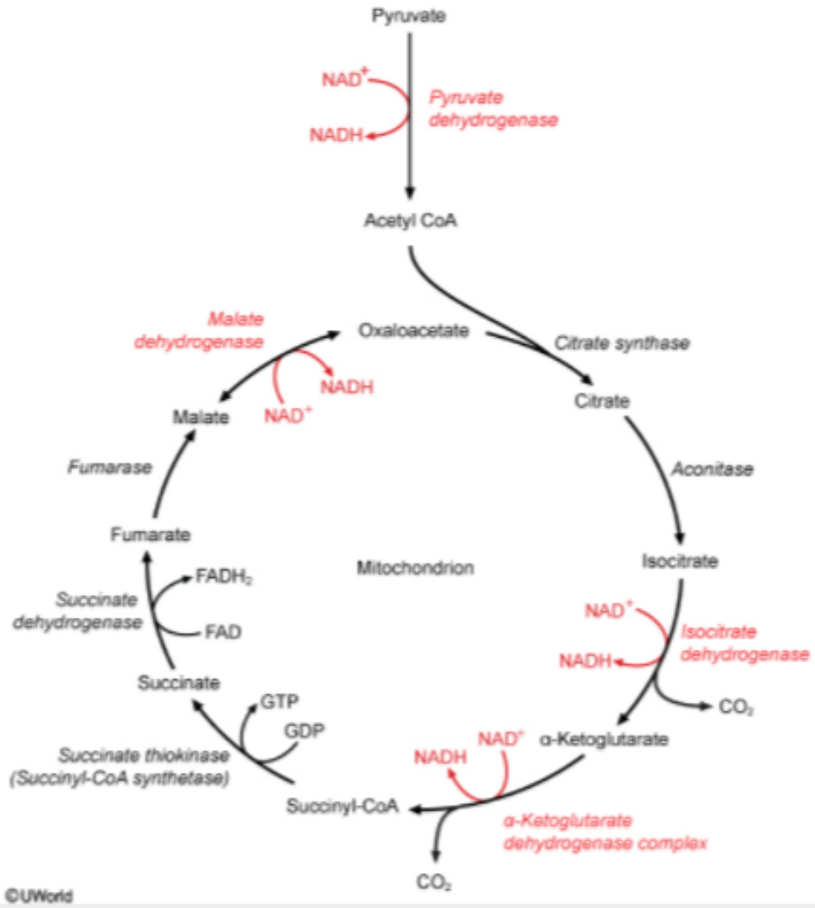
Niacin dependent enzymes in TCA cycle



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This patient likely has **pellagra**, a disease characterized by photosensitive dermatitis, diarrhea, and dementia occurring secondary to **vitamin B_3 (niacin) deficiency**. In the United States, pellagra is seen predominantly in malnourished populations (eg, patients with alcoholism or GI malabsorption).

Niacin is a precursor for nicotinamide adenine dinucleotide (**NAD**) and nicotinamide adenine dinucleotide phosphate (**NADP**), two important **cofactors** for many **dehydrogenase** and **reductase enzymes**. NAD is required for catabolic reactions (eg, glycolysis, beta-oxidation) as well as cell signaling and DNA repair, whereas NADP is necessary for many anabolic reactions such as fatty acid and cholesterol synthesis. NAD is a key constituent of the citric acid cycle; it serves as a cofactor for isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase.

(Choice A) Citrate synthase is an enzyme of the citric acid cycle; it does not require NAD or NADP as a cofactor.

(Choices B and D) Hexokinase and phosphoglycerate kinase are enzymes used in glycolysis; they do not require NAD or NADP as cofactors.

(Choice E) Succinate dehydrogenase is an enzyme of the citric acid cycle; it catalyzes the conversion of succinate to fumarate using flavin adenine dinucleotide (FAD) as a cofactor.

Educational objective:
Niacin is a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), two important cofactors for many dehydrogenase and reductase enzymes. Niacin deficiency results in pellagra (ie, diarrhea, dementia, and dermatitis).

References

- Pellagra: a non-eradicated old disease.

Biochemistry	Dermatology	Niacin deficiency
Subject	System	Topic

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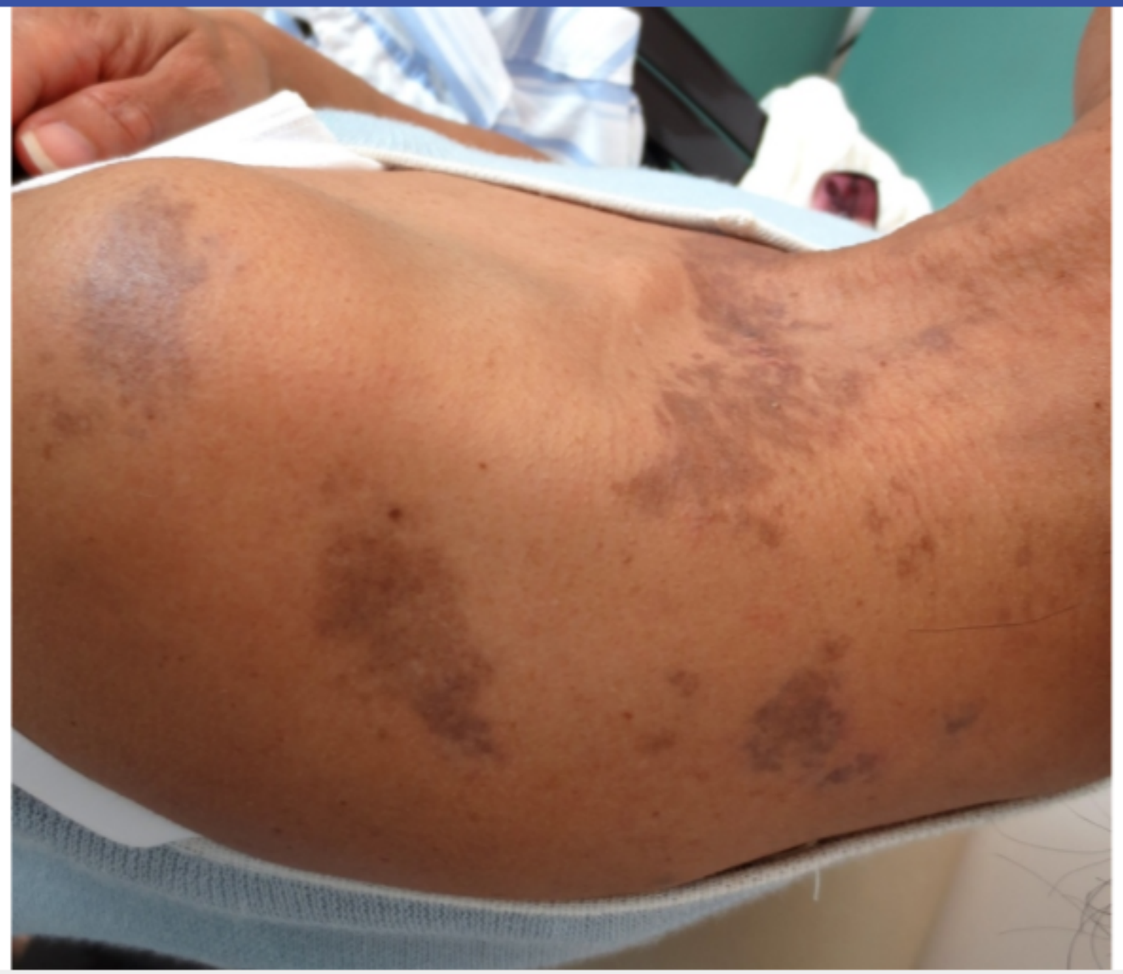
Exhibit Display



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A 24-year-old woman comes to the office for a preemployment medical evaluation. The patient has no known medical problems but reports that her skin bruises and scars easily. She says that most of her family members have a very "flexible" body, and her brother works in a circus as a contortionist. The patient takes no medications and has no allergies. She does not use tobacco, alcohol, or drugs. Physical examination findings are shown in the exhibit. This patient most likely has an inherited defect in which of the following proteins?

A. Collagen
B. Elastin
C. Fibrillin-1
D. Hyaluronic acid
E. Laminin
F. Proteoglycan

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Exhibit Display

Exhibit 1 Exhibit 2

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Exhibit Display

Exhibit 1 Exhibit 2

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- ✓ A. Collagen (76%)
- B. Elastin (14%)
- C. Fibrillin-1 (8%)
- D. Hyaluronic acid (0%)
- E. Laminin (0%)
- F. Proteoglycan (0%)

Omitted
Correct answer
A

76%
Answered correctly

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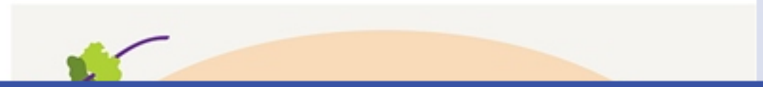
Explanation

Collagen synthesis



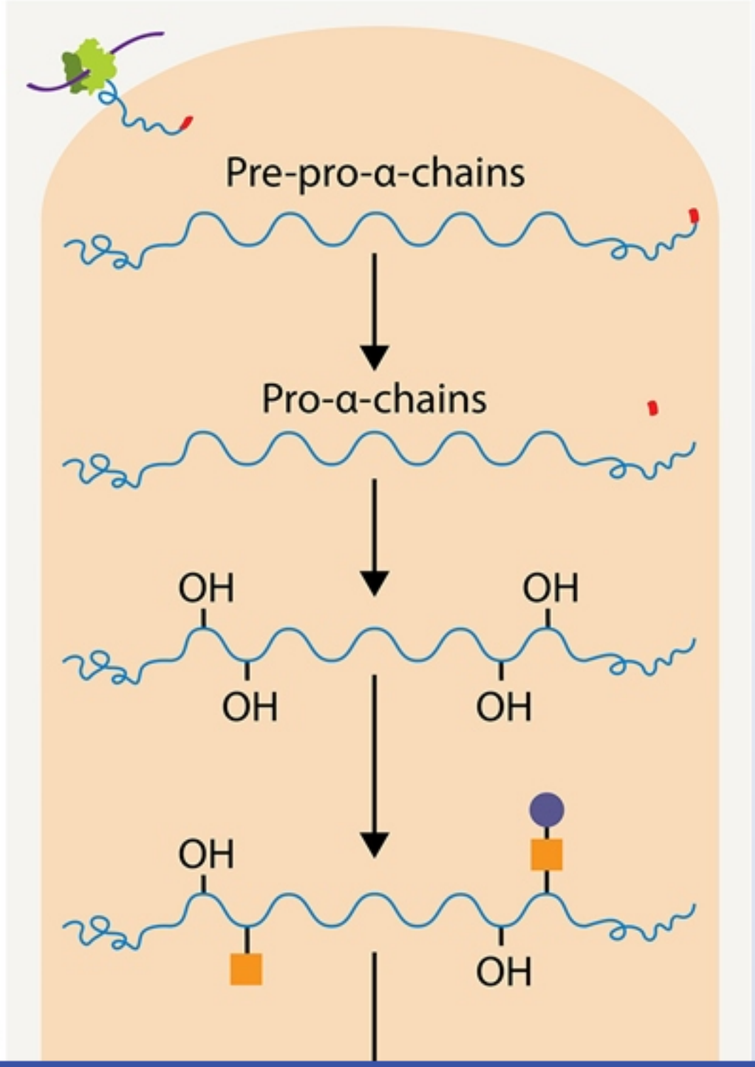
Collagen synthesis

Signal sequence directs growing polypeptide chain into endoplasmic reticulum

Signal sequence is cleaved

Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**

Glycosylation of selected hydroxylysine residues



Galactose

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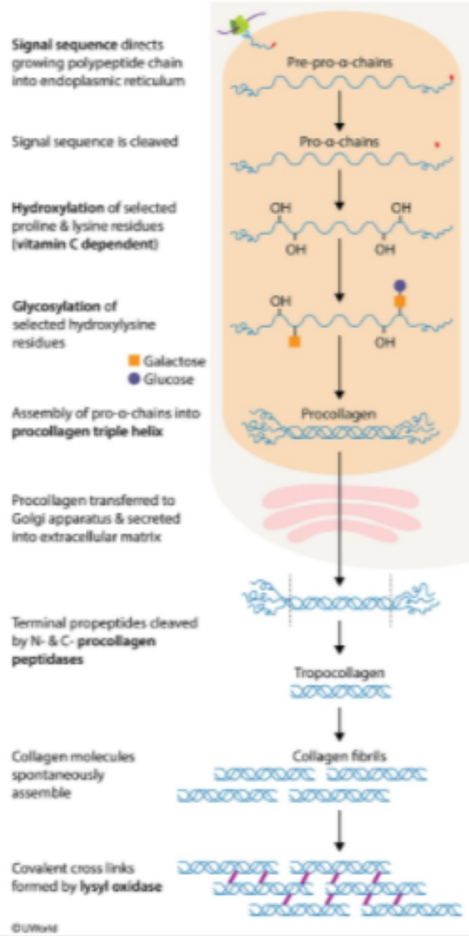
Exhibit Display

Collagen synthesis



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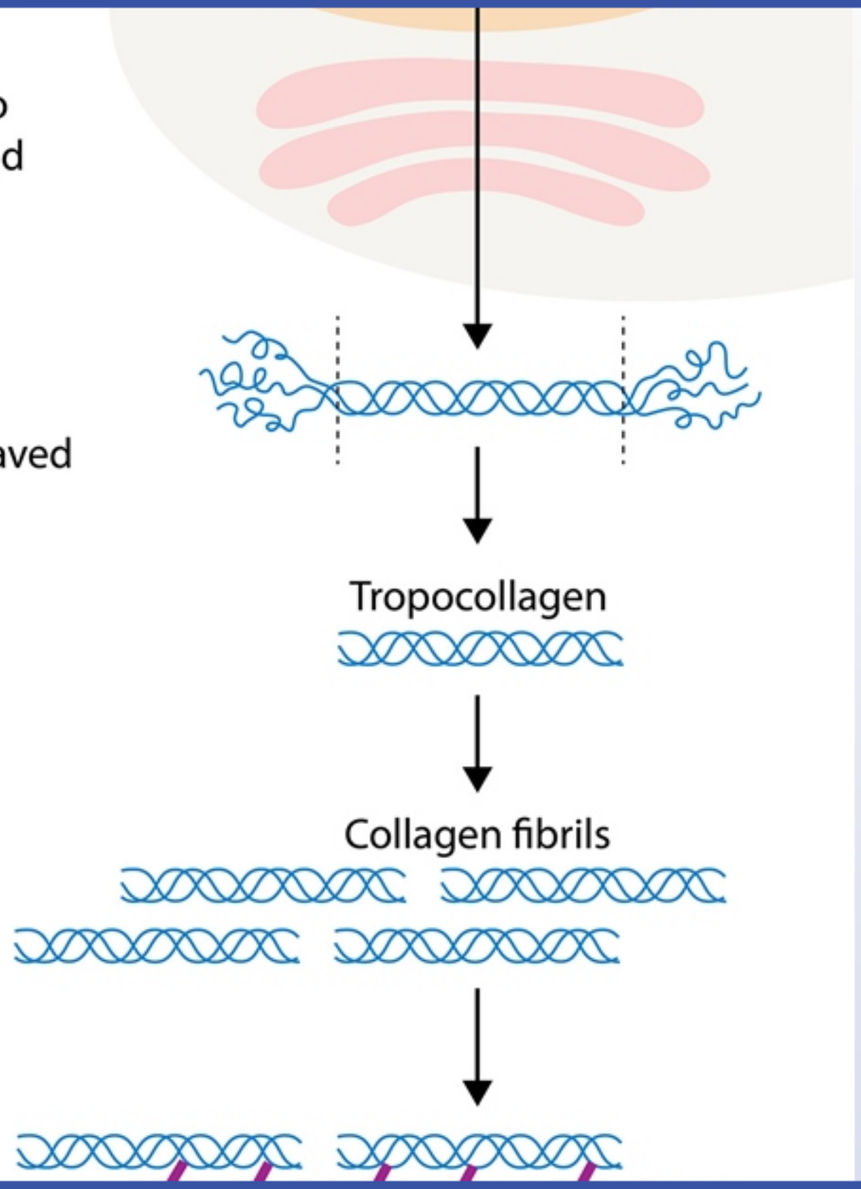

The extracellular matrix is a network of interstitial proteins that maintain normal tissue architecture. **Collagen** is a major component of **connective tissue** and consists of 3 polypeptide α chains held together by **hydrogen bonds** to form a ropelike triple helix structure (tropocollagen). **Lysyl oxidase** then forms covalent bonds between individual tropocollagen molecules, generating mature collagen fibers. The variation in amino acid sequences in the collagen α chains gives rise to collagen diversity in different tissues. Collagen types I, II, III, and V provide **tensile strength** in skin, bones, cartilage, tendons, and blood vessels.

Ehlers-Danlos syndrome (EDS) is a group of hereditary disorders involving a defect in collagen synthesis. EDS usually manifests clinically as **hypermobile joints**, **overelastic skin**, and fragile tissue susceptible to bruising, wounds, and hemarthrosis. Common mutations leading to EDS phenotypes include deficiencies of the lysyl hydroxylase and procollagen peptidase enzymes responsible for collagen synthesis.

(Choice B) Elastin, a fibrous protein in the connective tissue, is named for the elastic properties it imparts to skin, blood vessels, and lung alveoli. Elastin fibers can be stretched to several times their original length but will recoil when the stretching forces are withdrawn. Elastin is synthesized from the polypeptide precursor tropoelastin.

(Choice C) Fibrillin-1 is a major component of the microfibrils that form a sheath around elastin. Microfibrils are abundantly present in blood vessels and in the suspensory ligaments of the lens. Defects in the *fibrillin-1* gene cause classic autosomal dominant Marfan syndrome.

(Choice D) Hyaluronic acid is another major component of the soft tissue's extracellular matrix, including synovial fluid and skin. Exogenous injection can be used to restore viscoelasticity to the synovial fluid in osteoarthritis; soft-tissue fillers can also be used in patients concerned about age-related volume loss (eg, nasolabial folds).

(Choice E) Laminins are heterotrimeric glycoproteins that bind to type IV collagen underlying epithelial cells. They contribute to the organization and function of the basal lamina (basement membrane).

(Choice F) Proteoglycans are composed of glycosaminoglycans (GAGs), which provide compressibility to tissues. Patients with deficiencies in lysosomal enzymes cannot break down GAGs, resulting in mucopolysaccharidoses (eg, Hurler syndrome, Hunter syndrome) characterized by soft tissue and skeletal disease.

Educational objective:
Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disease associated with abnormal collagen formation. EDS usually manifests clinically as overflexible (hypermobile) joints, overelastic (hyperelastic) skin, and fragile tissue susceptible to bruising, wounding, and hemarthrosis.

from the polypeptide precursor tropoelastin.

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Ehlers-Danlos syndrome (EDS) is a heritable connective tissue disease associated with abnormal collagen formation. EDS usually manifests clinically as overflexible (hypermobile) joints, overelastic (hyperelastic) skin, and fragile tissue susceptible to bruising, wounding, and hemarthrosis.

References

- Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type.
- Ehlers-Danlos syndrome: how to diagnose and when to perform genetic tests.
- The Ehlers-Danlos syndrome, a disorder with many faces.

Biochemistry	Dermatology	Ehlers danlos syndrome
Subject	System	Topic

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An 8-year-old boy of Ashkenazi Jewish ancestry is brought to the office after developing reduced sensitivity to pain, impaired tear formation, and orthostatic hypotension. Familial dysautonomia is suspected due to the patient's symptoms and heritage. This disorder is caused by loss of function of the IKAP protein, which is essential for development and survival of sensory and autonomic neurons. *IKAP* gene sequencing reveals a single nucleotide substitution that causes a guanine residue to be replaced by adenine at the highlighted position in the normal gene sequence shown below. Exon sequences are represented by capital letters and introns by lowercase letters.

Which of the following is the most likely effect of this mutation?

A. Decreased mRNA export to the cytosol

B. Impaired ribosomal attachment to mRNA

C. Incorrect splicing of pre-mRNA

D. Increased degradation of mRNA by 5' exonucleases

E. Translation of the 3'-untranslated region of mRNA

Submit

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5'-GTACAAACATTGCTGCTGGGAAAGCCGCCGCCGCCACCATG
GGCTATGGGAGTGGTGGTAGCACTGGAGTTAACACCGAAATTG
GCAAGATCCGGGATGAAATGGTGG AACAGAACAGGAGAGAAC
ACCCCTTCAGCAAAAACTAGATGAATTTAAAGTCATCTCCCTTA
TTTGCATTGCAGGCTGGATCATAAATATTGGGCACTTCAATGAC
CCGGTTGATGGAGGGTCCTGGATCAGAGGTGCTATTTACTACT
TAAAATTGCAGTGGCCCTGGCTGTAGCAGGTGATTCCATTCCT
AAGgtctgcctgcagtcatcaccacctgcctggctctggaactcgcagaagaaaaatgcc
cattggaagcctcccgtctgtggaaacccttggttgtacttctgttatctgctcagacaagactgg
tacacttacaacaaaccagatgcagtctgcagGTACAAACATTGCTGCTGGGA
AAGCTATGGGAGTGGTGGTAGCAACTGGAGTTAAACCGAAATT
GGCAAGATCCGGGATGAAATGGTGGCAACAGAACAGGAAGAA
CACCCCTTCAGCAAAAACTAGATGAATTTGGGGAACAGCTTTCC
AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGACTTCAATGACCCGGTTCATGGAGgtcmgatcagaggtgctatttacta
ctttaaaattgcagtggccctggctgtagcagccattcctgaaggtctgcctgcagtcatcacac
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shown below. Exon sequences are represented by capital letters and introns by lowercase letters.

5'-GTACAAACATTGCTGCTGGGAAAGCCGCCGCCGCCACCATG
GGCTATGGGAGTGGTGGTAGCACTGGAGTTAACACCGAAATTG
GCAAGATCCGGGATGAAATGGTGG AACAGAACAGGAGAGAAC
ACCCCTTCAGCAAAAACTAGATGAATTTAAAGTCATCTCCCTTA
TTTGCATTGCAGGCTGGATCATAAATATTGGGCACTTCAATGAC
CCGGTTGATGGAGGGTCCTGGATCAGAGGTGCTATTTACTACT
TAAAATTGCAGTGGCCCTGGCTGTAGCAGGTGATTCCATTCCT
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cattggaagcctcccgtctgtggaaacccttggttgtacttctgttatctgctcagacaagactgg
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AAGCTATGGGAGTGGTGGTAGCAACTGGAGTTAAACCGAAATT
GGCAAGATCCGGGATGAAATGGTGGCAACAGAACAGGAAGAA
CACCCCTTCAGCAAAAACTAGATGAATTTGGGGAACAGCTTTCC
AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGACTTCAATGACCCGGTTCATGGAGgtcmgatcagaggtgctatttacta
ctttaaaattgcagtggccctggctgtagcagccattcctgaaggtctgcctgcagtcatcacac
ctgccGggctctGggaactcgcagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'

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Which of the following is the most likely effect of this mutation?

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tacacttacaacaaaccagatgcagtctgcagGTACAAACATTGCTGCTGGGA
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ctgccGggctctGggaactcgcagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'

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Which of the following is the most likely effect of this mutation?

A. Decreased mRNA export to the cytosol

B. Impaired ribosomal attachment to mRNA

C. Incorrect splicing of pre-mRNA

D. Increased degradation of mRNA by 5' exonucleases

E. Translation of the 3'-untranslated region of mRNA

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GGCAAGATCCGGGATGAAATGGTGGCAACAGAACAGGAAGAA
CACCCCTTCAGCAAAAACTAGATGAATTTGGGGAACAGCTTTCC
AAAGTCATCTCCCTTATTTGCATTGCAGTCTGGATCATAAATTTG
GGACTTCAATGACCCGGTTCATGGAGgtcmgatcagaggtgctatttacta
ctttaaaattgcagtggccctggctgtagcagccattcctgaaggtctgcctgcagtcatcacac
ctgccGggctctGggaactcgcagaatggcaaagaaaaatgccattgttcgaagcctcag
GTCTGTGGAAACCCTTGGTTGACTTCTGTTATCTGCTCAGACAG
ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'

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Which of the following is the most likely effect of this mutation?

A. Decreased mRNA export to the cytosol (2%)

B. Impaired ribosomal attachment to mRNA (4%)

✓ C. Incorrect splicing of pre-mRNA (86%)

D. Increased degradation of mRNA by 5' exonucleases (3%)

E. Translation of the 3'-untranslated region of mRNA (3%)

Omitted
Correct answer

86%
Answered correctly

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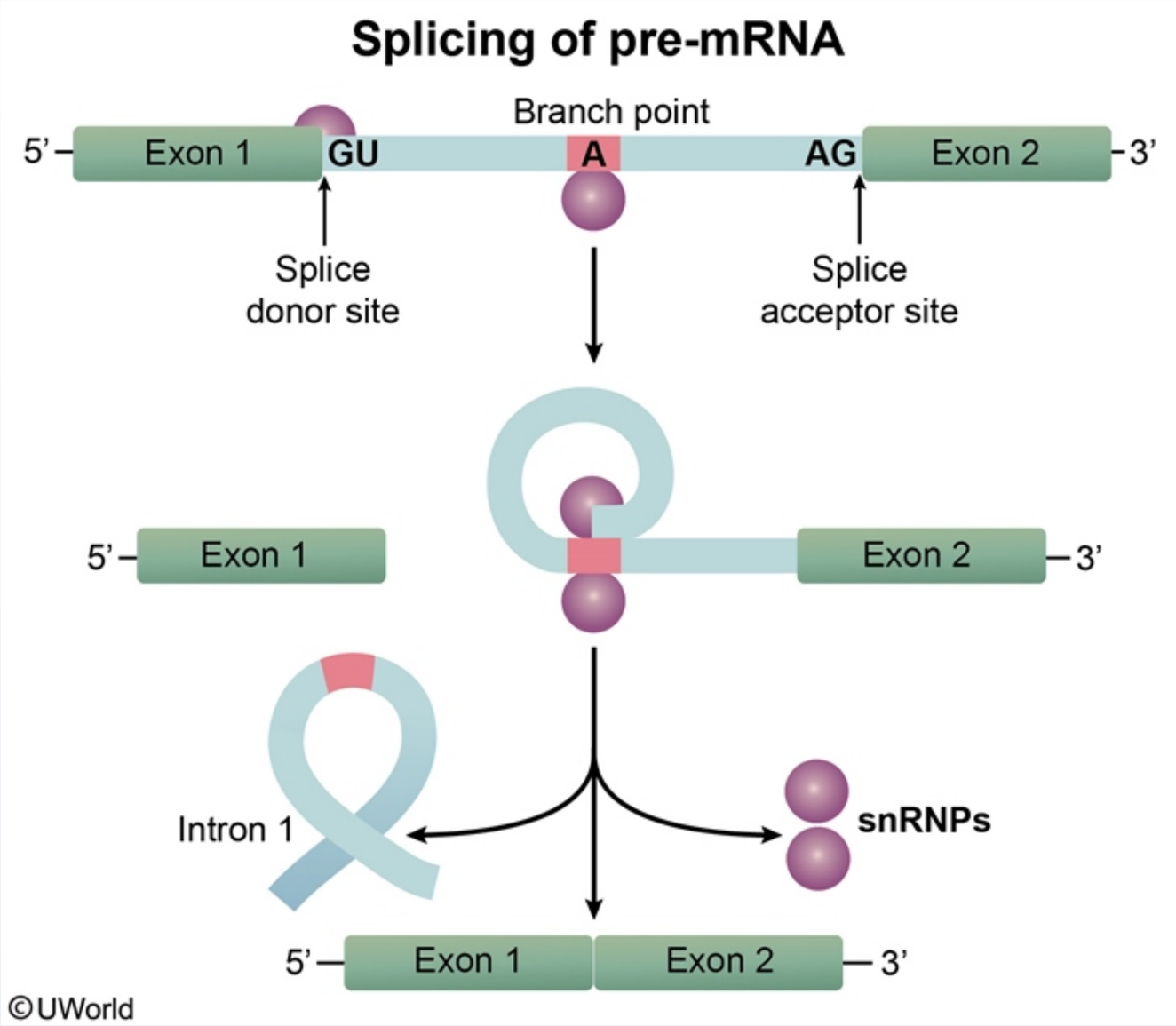

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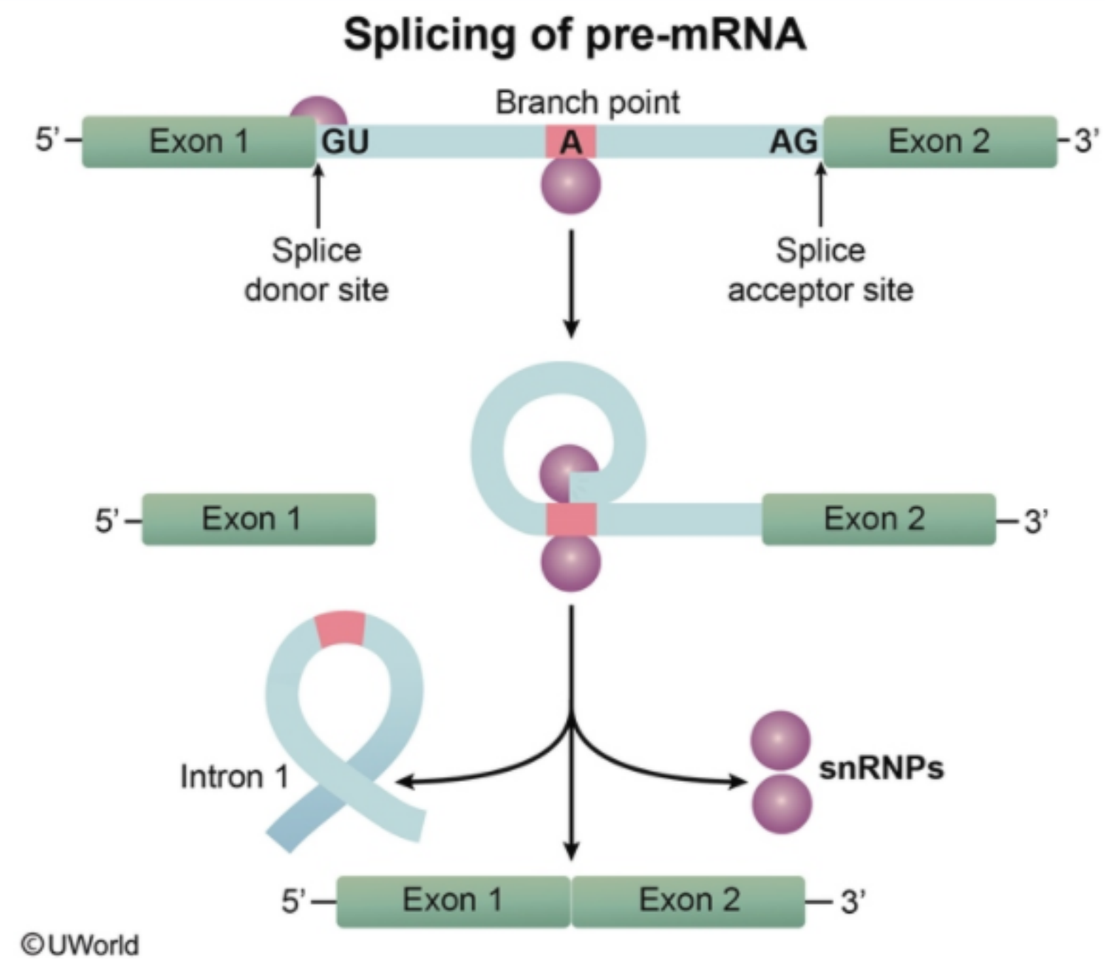

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Following transcription, pre-mRNA is the initial transcript that contains both intron and exon sequences. Before leaving the nucleus, pre-mRNA must be processed to mature mRNA by 3 post-transcriptional modifications: 5' methylguanosine capping, addition of a 3' polyadenine (Poly A) tail, and splicing.

Splicing is performed by **spliceosomes**, which are complexes of small nuclear ribonucleoproteins (snRNPs) and other proteins that assemble on pre-mRNA. Spliceosomes **remove introns** containing **GU** at the **5' splice site** and **AG** at the **3' splice site**. Initially, the 5' end of intron 1 (splice donor site) is cleaved and joined to the branch point. The freed 3'-OH of exon 1 then forms a phosphodiester bond with the 5'-phosphate at the splice acceptor site, joining exons 1 and 2. Mutations at splice sites may result in inappropriate removal of exons and retention of introns. This often leads to the formation of proteins with impaired structure and function as described in the case above.

(Choice A) Polyadenylation of the 3' end of mRNA is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA and helps it exit the nucleus.

(Choices B and D) In eukaryotes, translation is initiated when the small ribosomal subunit attaches to the 5' cap of mRNA and then scans for the AUG start codon within the Kozak consensus sequence. The 5' cap also protects against exonucleases and helps stabilize mRNA in the cytosol.

(Choice E) Termination of polypeptide synthesis occurs at the 3 stop codons (UAA, UAG, UGA) in mRNA. Mutations in stop codons (nonstop mutations) can result in continued and inappropriate translation of mRNA into the 3'-untranslated region, producing an extremely long, nonfunctional polypeptide.

Educational objective:
Splicing is performed by spliceosomes, which remove introns containing GU at the 5' splice site and AG at the 3' splice site. Splice site mutations may result in inappropriate removal of exons and retention of introns, leading to the formation of dysfunctional proteins.

References

- Familial dysautonomia is caused by mutations of the IKAP gene.
- RNA splicing: disease and therapy.
- The pathobiology of splicing.

A 40-year-old woman comes to the office with a 3-month history of progressive limitation of physical activity due to fatigue. She says, "I could barely walk from my car to your office." Past medical history is significant for a positive tuberculin skin test 7 months ago with a normal chest radiograph. She has been compliant with the prescribed treatment despite its bitter taste. Physical examination shows a tired-appearing woman with conjunctival and palmar pallor. Results of complete blood count are as follows:

Hemoglobin	9 g/dL
Hematocrit	28%
Mean corpuscular volume	72 fL

Bone marrow aspirate revealed the following representative sample under Prussian blue stain.

Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

A. δ-aminolevulinate dehydratase
B. δ-aminolevulinate synthase
C. Cystathionine synthase
D. Glucose-6-phosphate dehydrogenase
E. Pyruvate kinase

Submit

A 40-year-old woman comes to the office with a 3-month history of progressive limitation of physical activity due to fatigue. She says, "I could barely walk from my car to your office." Past medical history is significant for a positive tuberculin skin test 7 months ago with a normal chest radiograph. She has been compliant with the prescribed treatment despite its bitter taste. Physical examination shows a tired-appearing woman with conjunctival and palmar pallor. Results of complete blood count are as follows:

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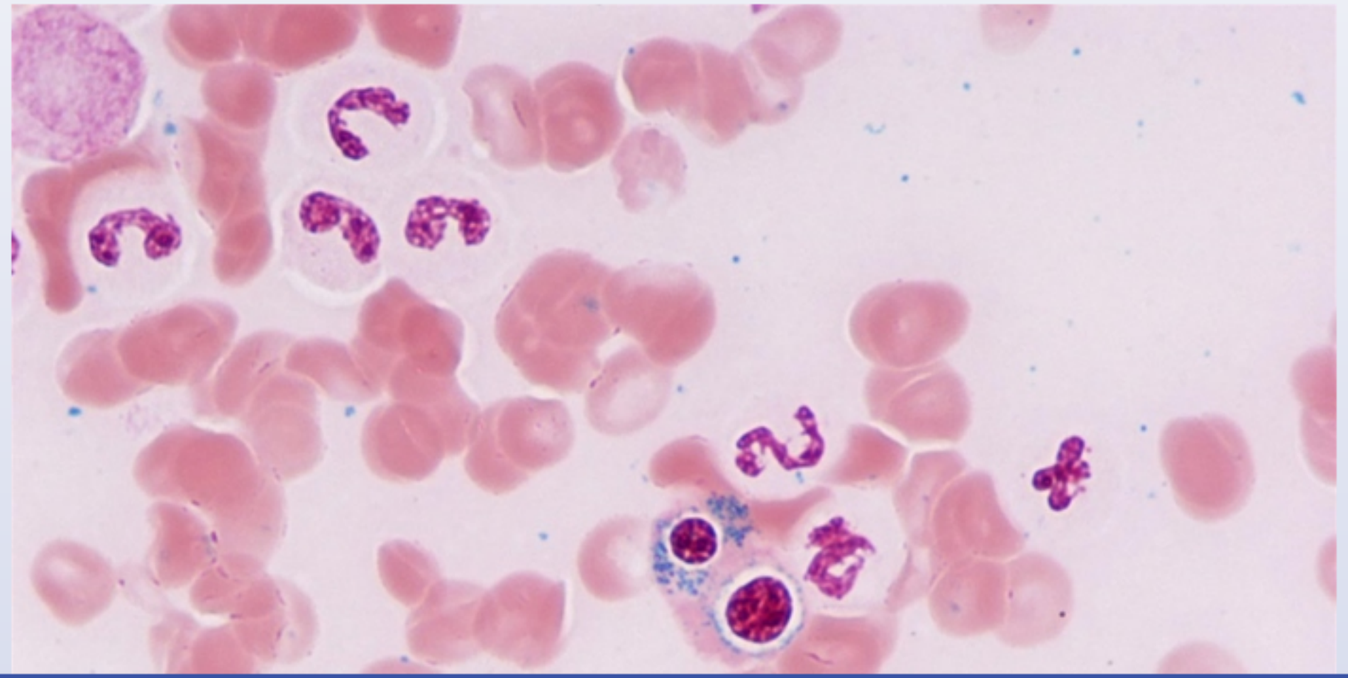

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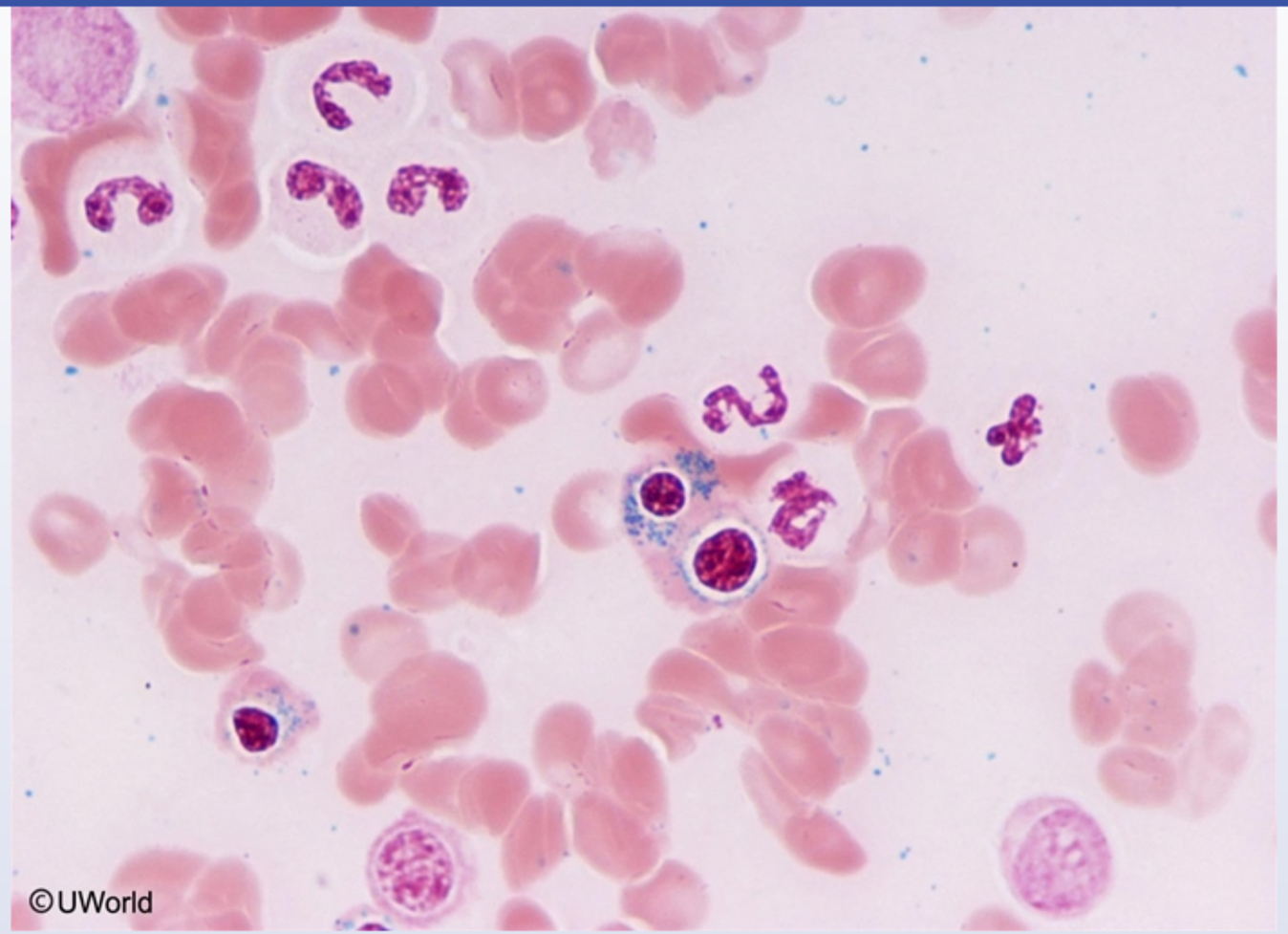

Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

- A. δ-aminolevulinate dehydratase
- B. δ-aminolevulinate synthase

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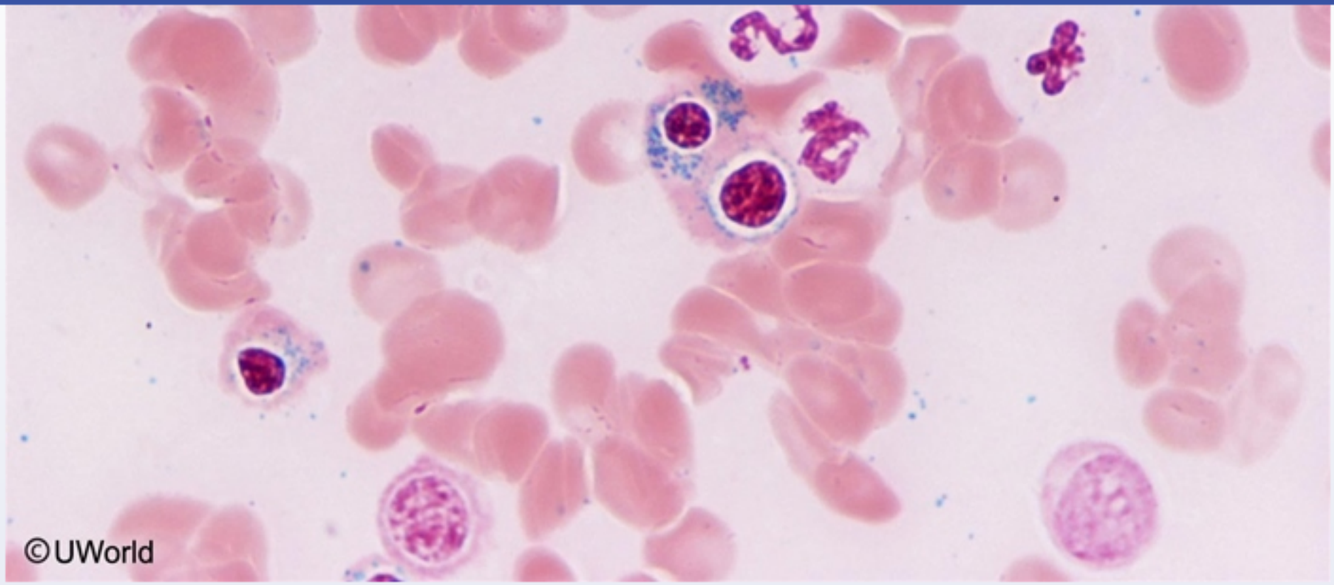

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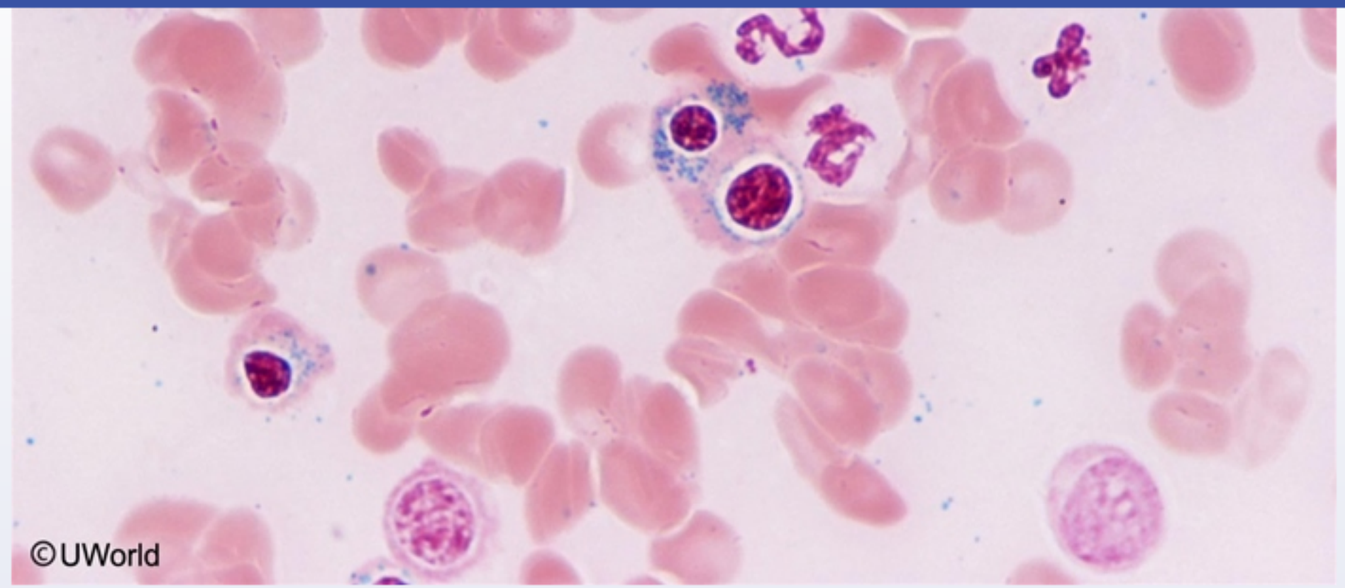
- B. δ-aminolevulinate synthase
- C. Cystathionine synthase
- D. Glucose-6-phosphate dehydrogenase
- E. Pyruvate kinase

Submit



Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

- A. δ-aminolevulinate dehydratase (17%)
- ✓ B. δ-aminolevulinate synthase (57%)
- C. Cystathionine synthase (6%)
- D. Glucose-6-phosphate dehydrogenase (15%)
- E. Pyruvate kinase (3%)

Omitted
Correct answer

57%
Answered correctly

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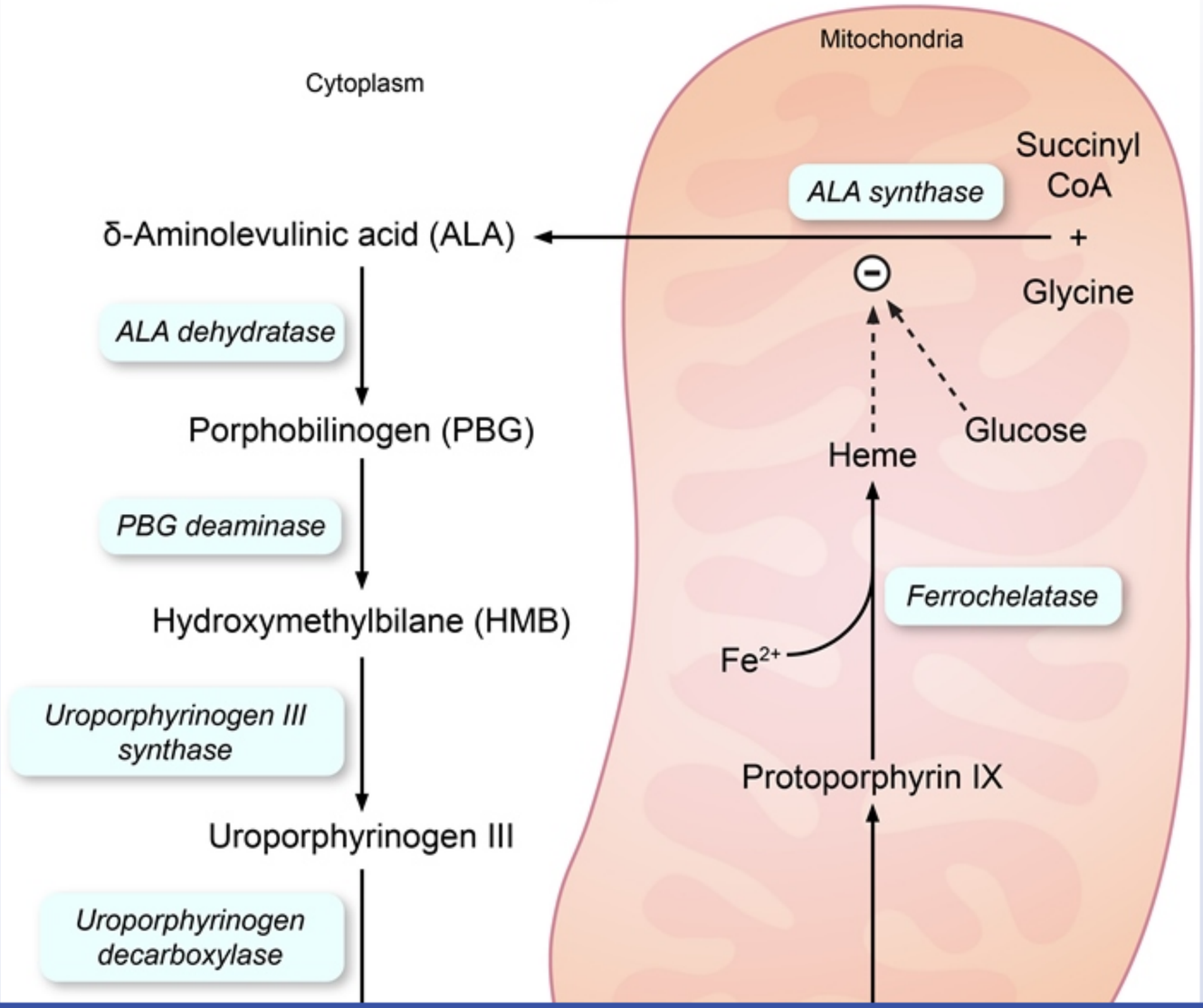
Heme synthesis



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This patient with latent tuberculosis has laboratory values and a bone marrow aspirate consistent with **sideroblastic anemia** due to isoniazid use. Sideroblastic anemia is diagnosed by bone-marrow examination with Prussian blue stain. Causes include X-linked sideroblastic anemia (due to an δ-aminolevulinate synthase mutation), myelodysplastic syndrome, alcohol abuse, copper deficiency, and certain medications (eg, isoniazid, chloramphenicol, linezolid).

Isoniazid directly inhibits the enzyme **pyridoxine phosphokinase**, which normally converts pyridoxine (vitamin B_6) to its active form, pyridoxal 5' phosphate. Pyridoxal 5' phosphate is a cofactor for **δ-aminolevulinic acid (ALA) synthase**, the enzyme that catalyzes the rate-limiting step in heme synthesis. Inhibition of this enzyme produces a **microcytic, hypochromic anemia**. Iron is transported to developing erythrocytes that cannot form heme, and its granules accumulate circumferentially around the nucleus, forming **ring sideroblasts**.

Because pyridoxal 5' phosphate is a cofactor for numerous enzymes, pyridoxine deficiency can also lead to dermatitis, stomatitis, neuropathy, and confusion. Therefore, pyridoxine is typically prescribed with isoniazid.

(Choice A) δ-aminolevulinate dehydratase is also involved in heme synthesis. Lead poisoning can cause anemia by directly inhibiting this enzyme.

(Choice C) Cystathionine synthase is a pyridoxine-dependent enzyme that catalyzes the formation of cystathionine from homocysteine. Cystathionine synthase deficiency results in homocystinuria, an autosomal recessive disorder characterized by a marfanoid body habitus and hypercoagulability.

(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency results in increased red blood cell susceptibility to oxidative stress (eg, infection, medication, fava beans), which triggers hemolysis. This results in a normocytic normochromic anemia with increased reticulocyte count and decreased haptoglobin.

(Choice E) Pyruvate kinase deficiency, an autosomal recessive disorder, results in a hemolytic anemia characterized by a normocytic normochromic anemia, reticulocytosis, and elevated indirect bilirubin.

Educational objective:
Isoniazid inhibits pyridoxine phosphokinase, leading to pyridoxine (vitamin B_6) deficiency. Pyridoxine's active form is the cofactor for δ-aminolevulinate synthase, the enzyme that catalyzes the rate-limiting step of heme synthesis. Inhibition of this step can result in sideroblastic

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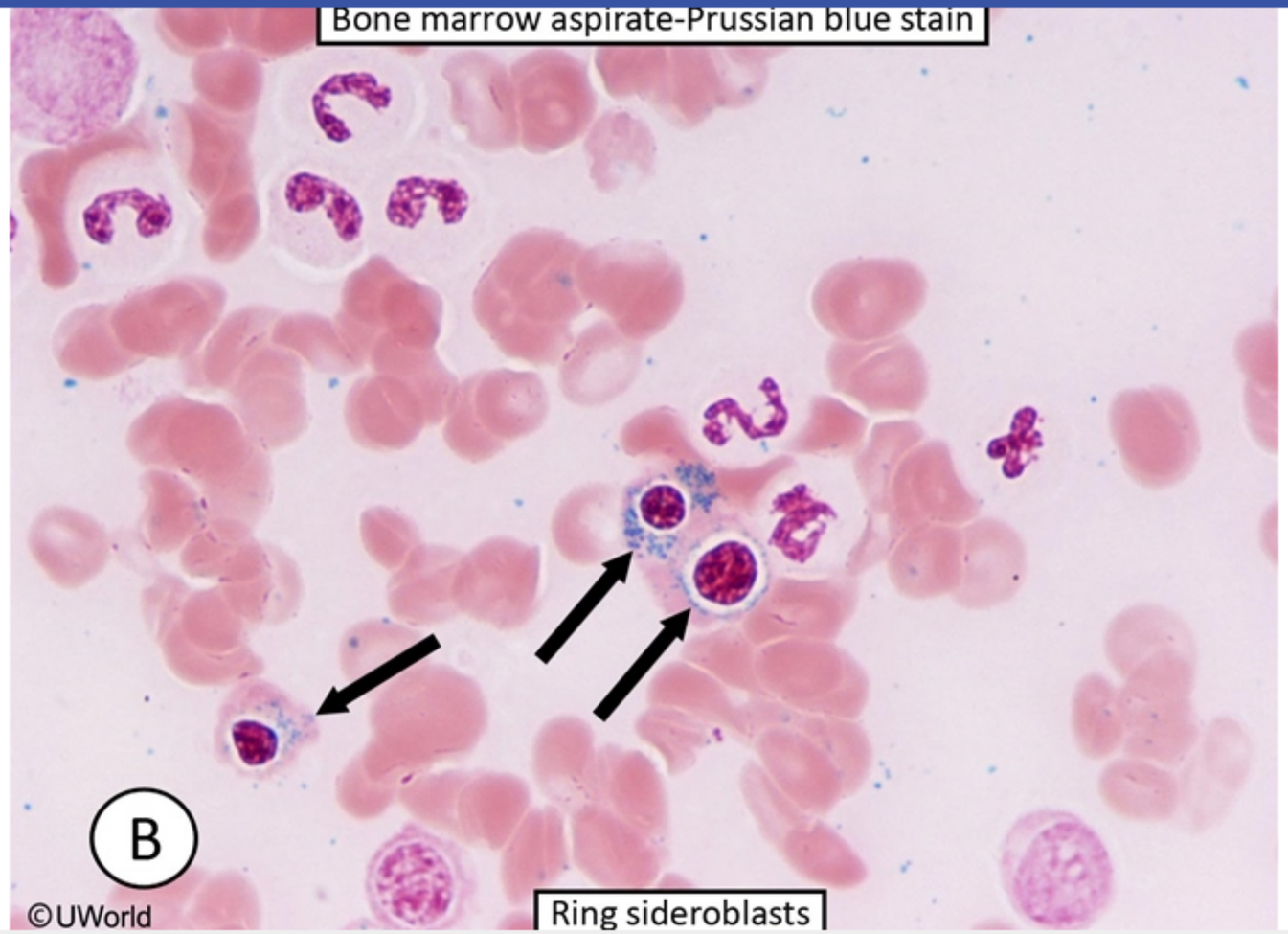

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aminolevulinate synthase, the enzyme that catalyzes the rate-limiting step of heme synthesis. Inhibition of this step can result in sideroblastic

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(Choice E) Pyruvate kinase deficiency, an autosomal recessive disorder, results in a hemolytic anemia characterized by a normocytic normochromic anemia, reticulocytosis, and elevated indirect bilirubin.

Educational objective:
Isoniazid inhibits pyridoxine phosphokinase, leading to pyridoxine (vitamin B_6) deficiency. Pyridoxine's active form is the cofactor for δ-aminolevulinate synthase, the enzyme that catalyzes the rate-limiting step of heme synthesis. Inhibition of this step can result in sideroblastic anemia.

References

- Sideroblastic anemia: diagnosis and management.
- Severe isoniazid related sideroblastic anemia.

Biochemistry	Hematology & Oncology	Sideroblastic anemia
Subject	System	Topic

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A 54-year-old man with a history of chronic kidney disease due to hypertension develops anemia. Evaluation reveals that the cause of anemia is erythropoietin deficiency. Erythropoietin increases the numbers of erythroid precursor cells in the bone marrow and induces heme production in erythrocyte precursors. In this patient, mature erythrocytes are found that are unable to synthesize heme even though they contain detectable levels of cytoplasmic enzymes involved in heme synthesis. Lack of which of the following cellular organelles best explains this phenomenon?

- A. Endoplasmic reticulum
- B. Golgi apparatus
- C. Mitochondria
- D. Nucleus
- E. Peroxisomes
- F. Proteasomes

Submit

A 54-year-old man with a history of chronic kidney disease due to hypertension develops anemia. Evaluation reveals that the cause of anemia is erythropoietin deficiency. Erythropoietin increases the numbers of erythroid precursor cells in the bone marrow and induces heme production in erythrocyte precursors. In this patient, mature erythrocytes are found that are unable to synthesize heme even though they contain detectable levels of cytoplasmic enzymes involved in heme synthesis. Lack of which of the following cellular organelles best explains this phenomenon?

- A. Endoplasmic reticulum (14%)
- B. Golgi apparatus (5%)
- ✓ C. Mitochondria (64%)
- D. Nucleus (10%)
- E. Peroxisomes (3%)
- F. Proteasomes (1%)

Omitted
Correct answer
C

64%
Answered correctly

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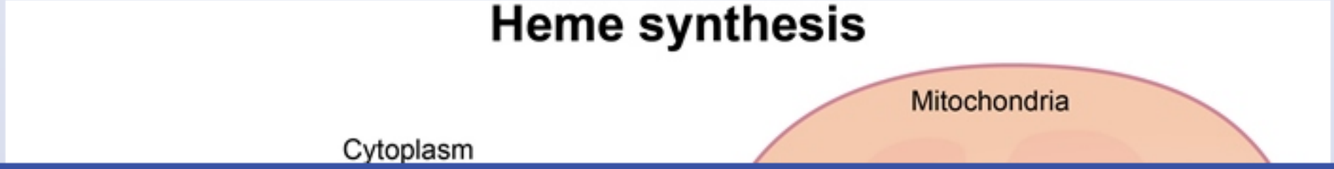
Time Spent

03/03/2020
Last Updated

Explanation



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Heme synthesis

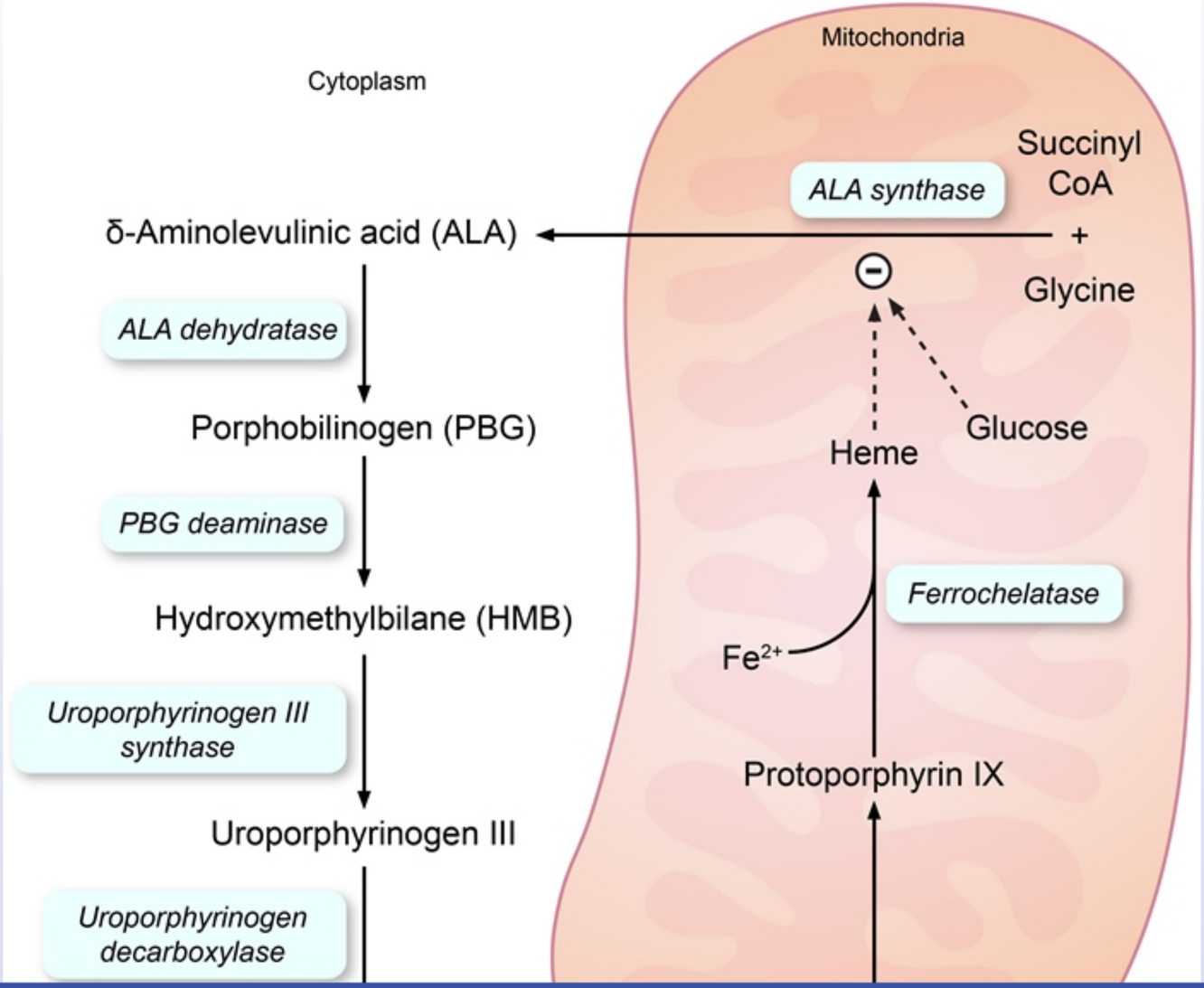

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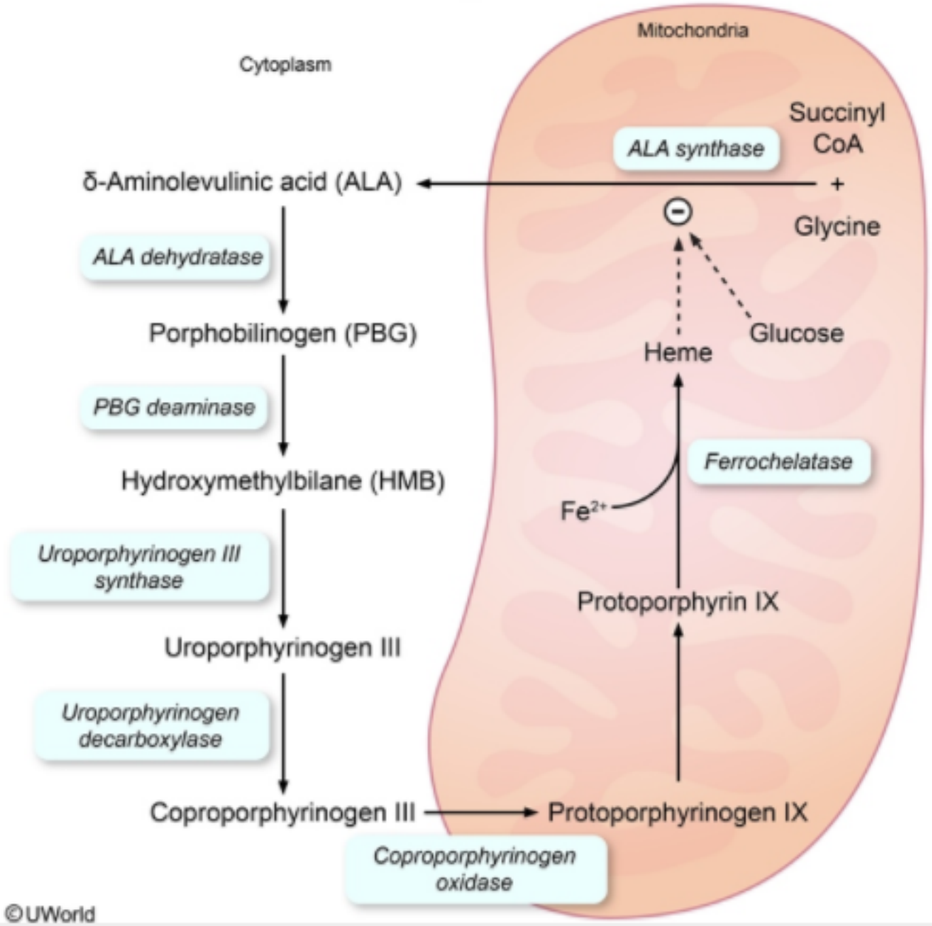
Exhibit Display

Heme synthesis



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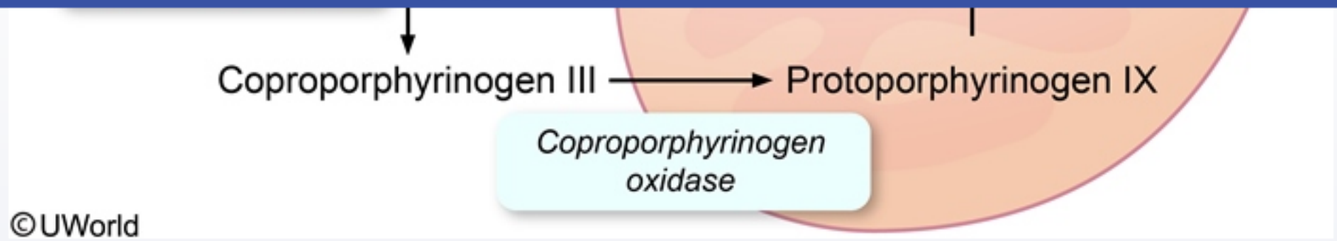

Heme synthesis occurs partly in the mitochondria and partly in the cytoplasm of erythrocytes. **Mitochondria** are necessary for the first and the final 3 steps. Erythrocyte precursors divide a number of times before finally losing their nuclei and mitochondria and forming mature red blood cells that survive for about 120 days (4 months). When erythrocytes lose their mitochondria, they lose the ability to generate heme and therefore hemoglobin.

Heme is synthesized in virtually every organ, but the principal sites of synthesis are erythrocyte precursor cells (located in the bone marrow) and hepatocytes (use heme in microsomal cytochrome P450 system).

(Choices A, B, and D) Although mature erythrocytes do not contain a nucleus, a Golgi apparatus, or an endoplasmic reticulum, their cytoplasm still contains residual amounts of the enzymes necessary for heme synthesis. Therefore, the lack of mitochondria (and their associated heme biosynthetic enzymes) is a better explanation for the lack of heme synthesis.

(Choices E and F) Proteasomes are involved in protein recycling and peroxisomes are involved in fatty acid catabolism. These organelles typically disappear during erythrocyte development.

Educational objective:
Maturing erythrocytes lose their ability to synthesize heme when they lose their mitochondria, which are necessary for the first and final 3 steps of heme synthesis.

Biochemistry	Hematology & Oncology	Heme metabolism
Subject	System	Topic

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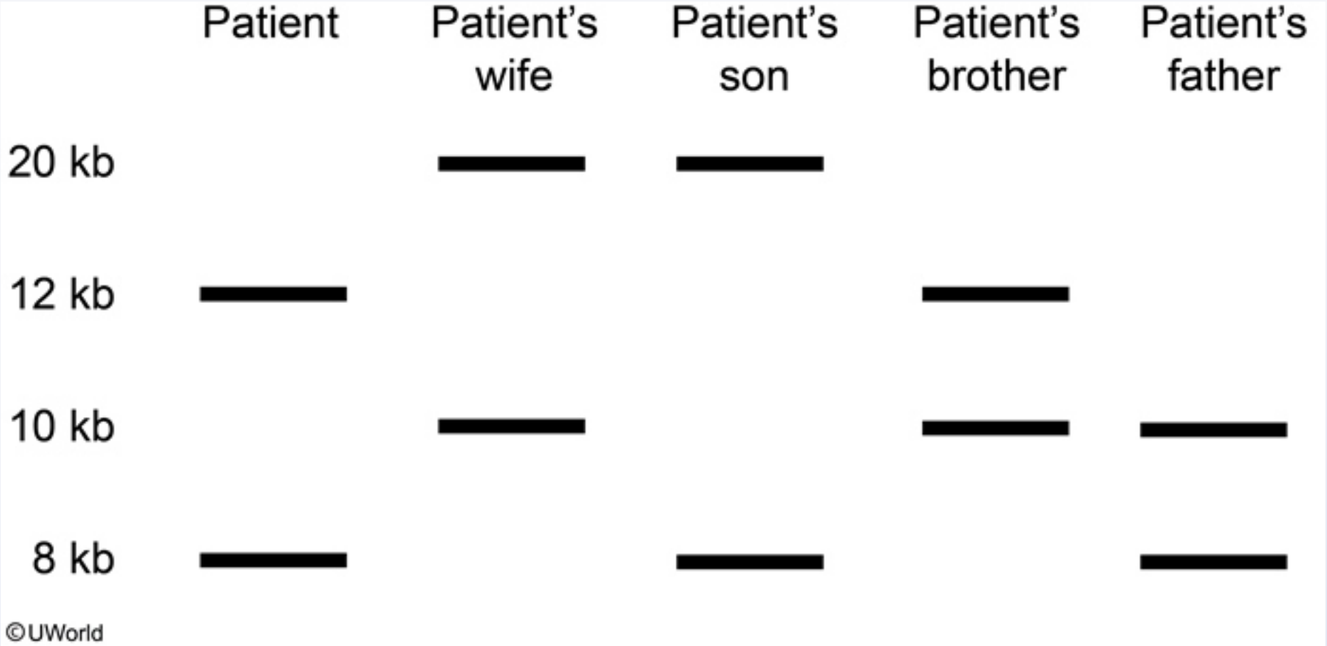
A 34-year-old man is found to have an LDL level of 310 mg/dL and a normal serum triglyceride level. His father suffered a myocardial infarction at age 39, and his paternal grandfather died of a heart attack at age 40. The patient's wife has a normal lipid profile. DNA samples are obtained from several family members for genetic analysis. Southern blotting of restriction fragments from a region containing the LDL receptor gene shows the following pattern:



Which of the following statements best describes the DNA analysis results?

- A. The disease is transmitted in an X-linked recessive fashion
- B. The mutation is probably located in the 10 kb band
- C. The mutation is probably located in the 12 kb band

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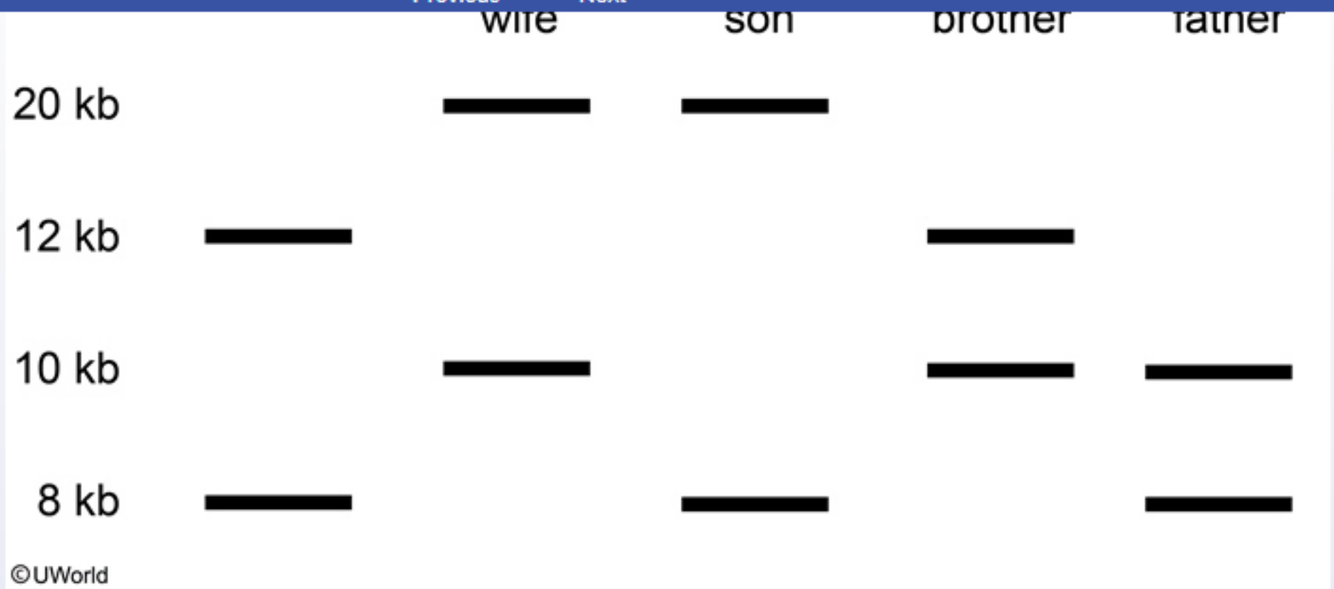

Which of the following statements best describes the DNA analysis results?

- A. The disease is transmitted in an X-linked recessive fashion
- B. The mutation is probably located in the 10 kb band
- C. The mutation is probably located in the 12 kb band
- D. The patient's brother most likely inherited the mutation
- E. The patient's son most likely inherited the mutation

Submit

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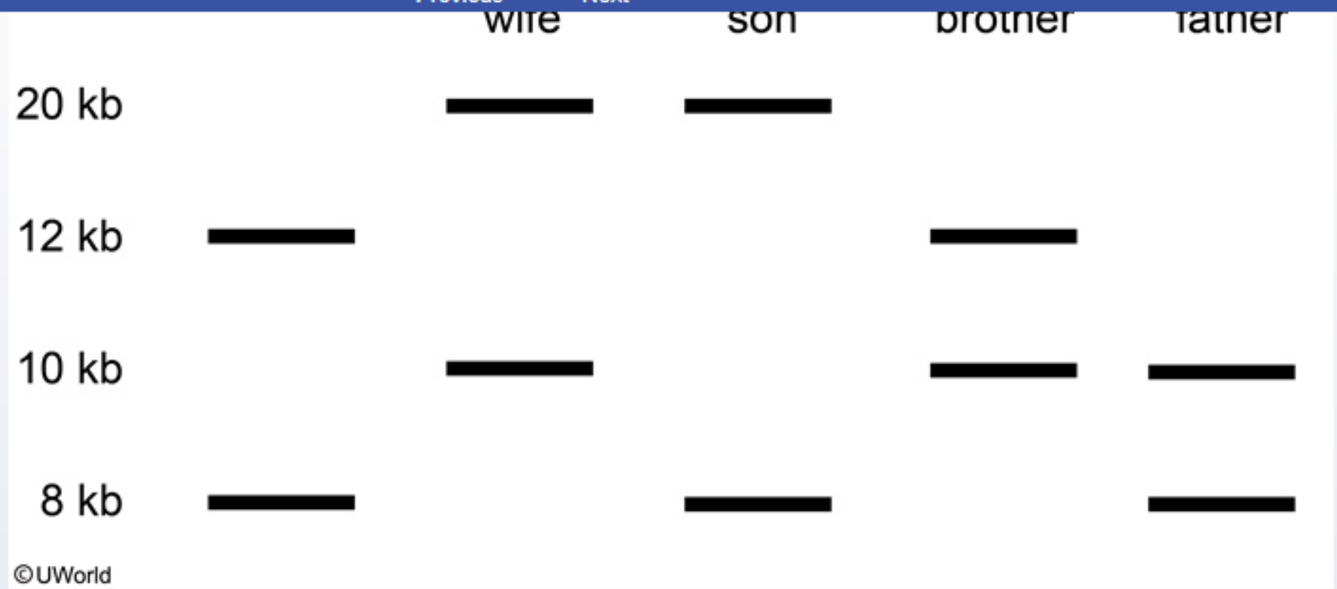

Which of the following statements best describes the DNA analysis results?

- A. The disease is transmitted in an X-linked recessive fashion (3%)
- B. The mutation is probably located in the 10 kb band (1%)
- C. The mutation is probably located in the 12 kb band (1%)
- D. The patient's brother most likely inherited the mutation (2%)
- ✓ E. The patient's son most likely inherited the mutation (91%)

Omitted
Correct answer

91%
Answered correctly

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Time Spent

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Last Updated

This patient most likely has **heterozygous familial hypercholesterolemia**, an autosomal dominant LDL receptor defect that causes **high LDL levels** and increases the risk of **premature atherosclerosis**. *Homozygous* familial hypercholesterolemia (a rarer and more severe form of the disease due to inheritance of 2 defective LDL receptor alleles) often presents with coronary heart disease in childhood/adolescence.

Southern blotting is a technique that can be used to detect DNA mutations. The process involves the following steps:

1. DNA extraction from the individual's cells
2. Restriction endonuclease digestion of the DNA sample into fragments
3. Gel electrophoresis to separate the various sizes of DNA fragments; larger fragments move slowly and shorter fragments move faster
4. DNA probe (a single-stranded segment of labeled DNA complementary to the gene of interest) to identify the target gene

Once the gene of interest is identified by the DNA probe, various family members' Southern blots can be compared. Because **both** the patient and his father are affected, the common DNA segment between them (**8 kb segment**) most likely represents the mutated gene. The patient's **son** also has the 8 kb segment, meaning that he is probably affected as well.

(Choice A) Familial hypercholesterolemia is an autosomal dominant disorder. X-linked recessive mutations are transmitted from unaffected carrier mothers to their sons. Father-to-son transmission does not occur.

(Choices B and D) The patient (affected by the disease) does not possess the 10 kb segment, so this segment does not correspond to the mutated gene. The patient's brother inherited the 10 kb segment from his father (not the 8kb mutated segment), so he would not be affected.

(Choice C) The patient and his brother, but not their father, have a 12 kb segment on Southern blot analysis. Therefore, this segment was likely inherited from the mother and does not carry the mutation.

Educational objective:
Southern blotting is a technique used to identify DNA mutations. It involves restriction endonuclease digestion of sample DNA, gel electrophoresis, and gene identification with a labeled DNA probe.

References

- Genetic defects causing familial hypercholesterolaemia: identification of deletions and duplications in the LDL-receptor gene and summary of all mutations found in patients attending the Hammersmith Hospital Lipid Clinic.

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2. Restriction endonuclease digestion of the DNA sample into fragments
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Biochemistry	Cardiovascular System	Rflp
Subject	System	Topic

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A 22-year-old woman comes to the hospital due to a 5-day history of nausea, constipation, and severe, poorly localized abdominal pain. She also reports anxiety, difficulty concentrating, poor sleep quality, and tingling of the limbs. The patient has had several similar episodes in the past. She does not take any medications or use tobacco, alcohol, or illicit drugs. The patient has been restricting her diet to lose weight. On examination, the abdomen is soft, nontender, and nondistended. Bowel sounds are decreased. The patient receives an intravenous infusion of a heme preparation that leads to rapid resolution of her symptoms. The improvement in symptoms is most likely due to treatment-induced downregulation of which of the following enzymes?

A. Aminolevulinate dehydratase
B. Aminolevulinate synthase
C. Bilirubin glucuronyl transferase
D. Ferrochelatase
E. Porphobilinogen deaminase

Submit

A 22-year-old woman comes to the hospital due to a 5-day history of nausea, constipation, and severe, poorly localized abdominal pain. She also reports anxiety, difficulty concentrating, poor sleep quality, and tingling of the limbs. The patient has had several similar episodes in the past. She does not take any medications or use tobacco, alcohol, or illicit drugs. The patient has been restricting her diet to lose weight. On examination, the abdomen is soft, nontender, and nondistended. Bowel sounds are decreased. The patient receives an intravenous infusion of a heme preparation that leads to rapid resolution of her symptoms. The improvement in symptoms is most likely due to treatment-induced downregulation of which of the following enzymes?

- A. Aminolevulinate dehydratase (9%)
- ✓ B. Aminolevulinate synthase (52%)
- C. Bilirubin glucuronyl transferase (4%)
- D. Ferrochelatase (12%)
- E. Porphobilinogen deaminase (19%)

Omitted
Correct answer
B

52%
Answered correctly

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Time Spent

01/21/2020
Last Updated

Explanation

Acute intermittent porphyria

CYP450 inducers
- Barbiturates
- Antiepileptics

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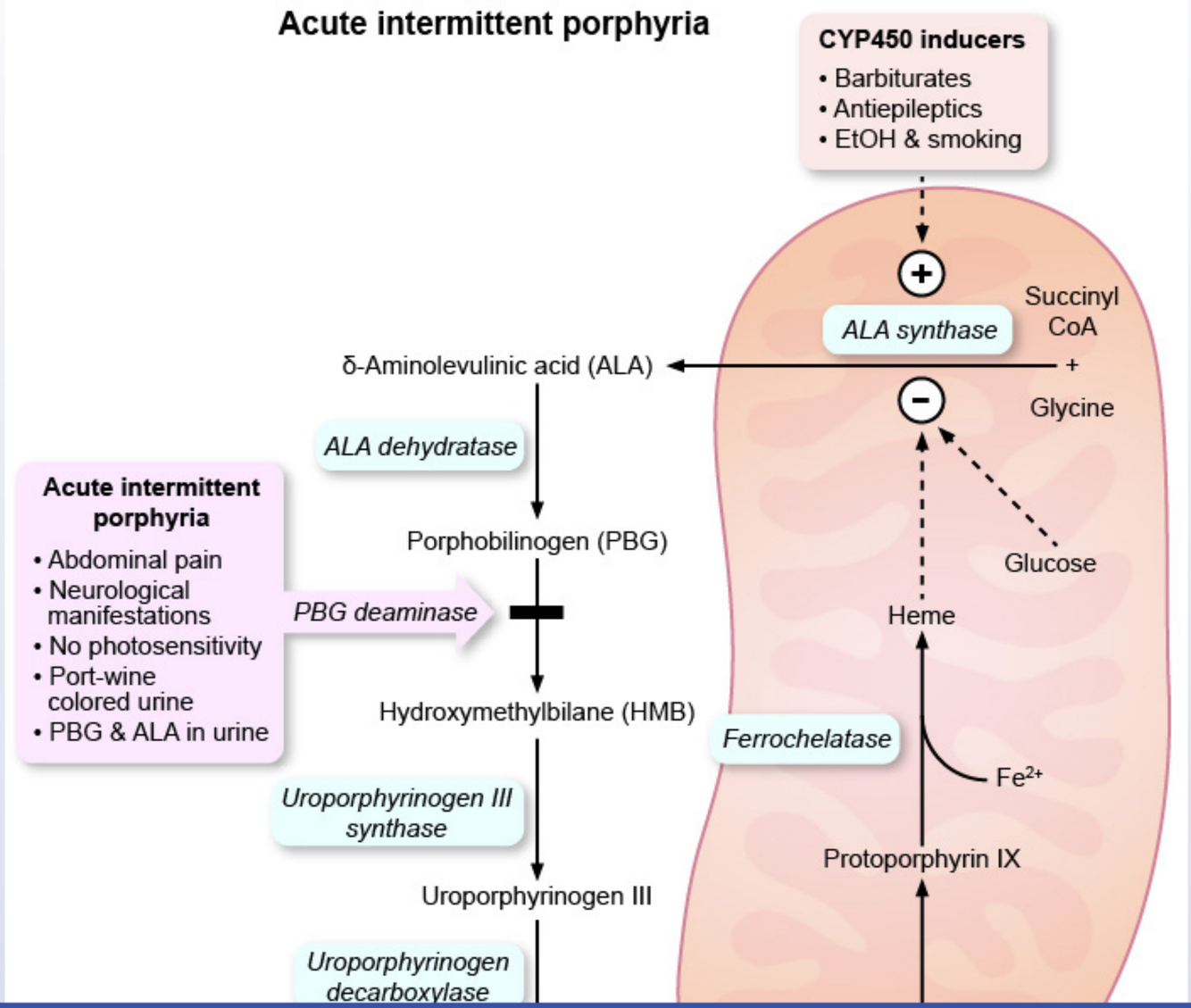

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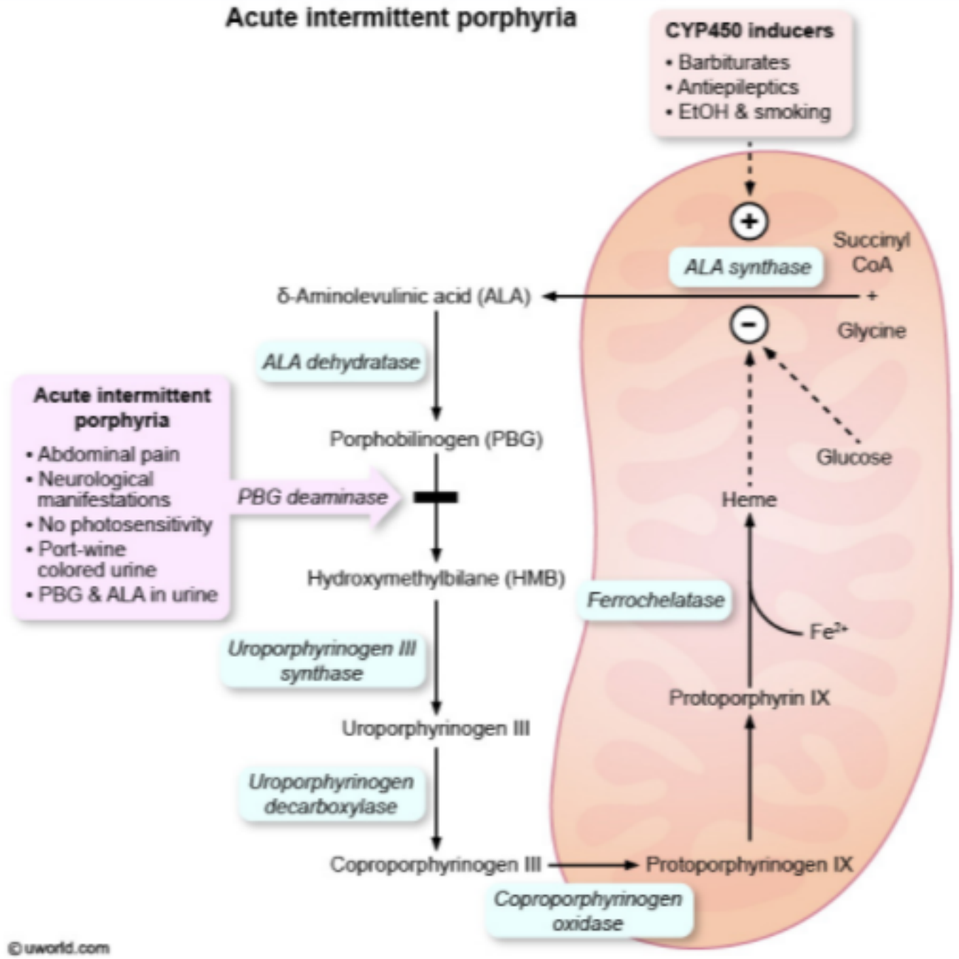

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decarboxylase

This patient with neurologic symptoms (eg, tingling, difficulty concentrating) and recurrent episodes of nonspecific abdominal pain likely has **acute intermittent porphyria** (AIP), an autosomal dominant disease characterized by **porphobilinogen (PBG) deaminase** deficiency. Management of AIP attacks includes infusion of hemin, which downregulates hepatic **aminolevulinate (ALA) synthase** (rate-limiting enzyme in hepatic pathway of heme synthesis).

Heme, a porphyrin, is synthesized in the liver for use in the cytochrome p450 enzyme system and in the bone marrow for hemoglobin use (these 2 synthesis pathways are regulated differently). A deficiency in any of the enzymes responsible for porphyrin synthesis can result in porphyria. Clinical manifestations result from the accumulation of porphyrin precursors in blood, tissues, and urine. AIP attacks, which are characterized by acute abdominal pain and neurologic symptoms, are due to accumulation of **ALA** and **PBG**, generally resulting from a combination of 2 factors:

- PBG deaminase deficiency (inherited)
- ALA synthase induction, typically precipitated by certain medications (eg, phenobarbital, griseofulvin, phenytoin), alcohol use, smoking, progesterone (eg, puberty), or a low-calorie diet (as seen with this patient)

Glucose or **hemin** inhibit ALA synthase and are used in AIP management. PBG deaminase deficiency by itself is generally not sufficient for development of AIP attacks (many patients with PBG deaminase deficiency are asymptomatic), and PBG deaminase enzyme activity is not directly affected by hemin infusion **(Choice E)**.

(Choices A and D) Deficiencies of ALA dehydratase and ferrochelatase (inhibited by lead) are seen with lead poisoning. Ferrochelatase deficiency is also seen with erythropoietic protoporphyria, characterized by cutaneous photosensitivity beginning in early childhood.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme that is responsible for the conjugation of bilirubin (byproduct of heme catabolism) with glucuronide, a polar molecule that improves bilirubin solubility for subsequent biliary excretion. A decrease in glucuronyl transferase activity results in unconjugated hyperbilirubinemia.

Educational objective:
Acute intermittent porphyria attacks are due to the accumulation of aminolevulinate (ALA) and porphobilinogen (PBG), resulting from inherited PBG deaminase deficiency combined with ALA synthase induction (typically due to certain medications, alcohol use, or a low-calorie diet). Management with glucose or hemin inhibits ALA synthase activity.

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Biochemistry	Hematology & Oncology	Heme metabolism
Subject	System	Topic

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A 15-year-old boy is found to have unexplained erythrocytosis on routine laboratory analysis. Evaluation of his immediate family shows that his father and sister also have elevated red cell levels. Genetic sequencing of the β-globin gene is performed in the affected family members. The results show a single base substitution at amino acid position 82 that replaces the normal lysine residue with methionine. Further analysis shows that this amino acid replacement impairs the ionic interaction between the β-subunit and 2,3-bisphosphoglycerate. As a result of this mutation, the patient's hemoglobin will be most similar to which of the following hemoglobin types?

A. Hemoglobin A_{1c}
B. Hemoglobin C
C. Hemoglobin F
D. Hemoglobin H
E. Hemoglobin S

Submit

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A. Hemoglobin A_{1c} (2%)

B. Hemoglobin C (11%)

✓ C. Hemoglobin F (70%)

D. Hemoglobin H (3%)

E. Hemoglobin S (12%)

Omitted
Correct answer
C

70%
Answered correctly

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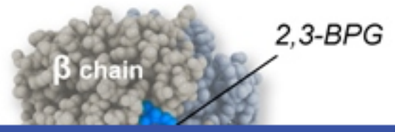
03/15/2020
Last Updated

Explanation

2,3-bisphosphoglycerate and hemoglobin binding



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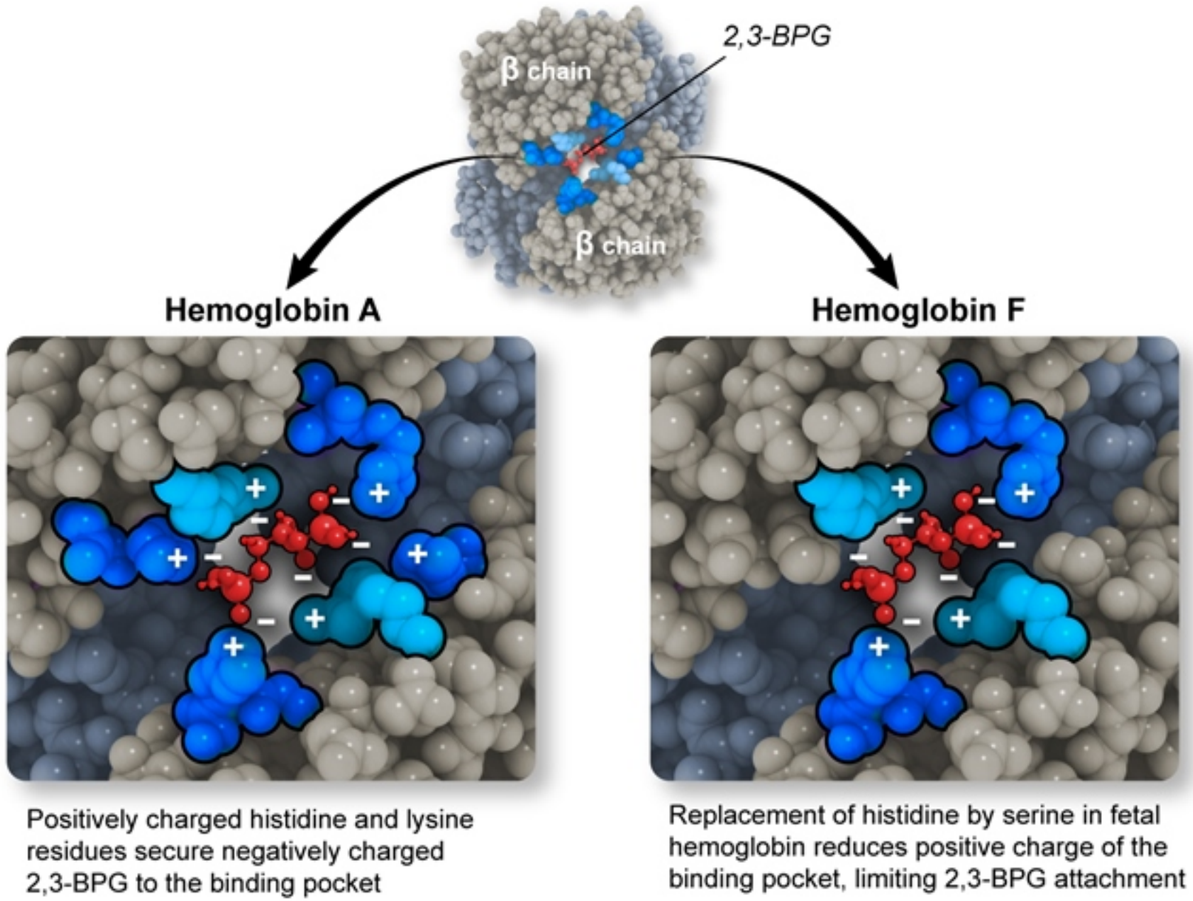
2,3-bisphosphoglycerate and hemoglobin binding



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This patient most likely has **familial erythrocytosis** due to a β-globin mutation resulting in reduced binding of **2,3-bisphosphoglycerate** (2,3-BPG). 2,3-BPG is synthesized from glycolytic intermediates and binds strongly to deoxyhemoglobin in a pocket formed between the 2 beta chains. This binding reduces the oxygen affinity of hemoglobin, allowing more oxygen to diffuse into the peripheral tissues. The hemoglobin 2,3-

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This patient most likely has **familial erythrocytosis** due to a β-globin mutation resulting in reduced binding of **2,3-bisphosphoglycerate** (2,3-BPG). 2,3-BPG is synthesized from glycolytic intermediates and binds strongly to deoxyhemoglobin in a pocket formed between the 2 beta chains. This binding reduces the oxygen affinity of hemoglobin, allowing more oxygen to diffuse into the peripheral tissues. The hemoglobin 2,3-BPG binding pocket contains positively charged amino acids (eg, histidine and lysine) that attract the negatively charged phosphate groups in 2,3-BPG. Mutations that decrease the positive charge of the binding site decrease 2,3-BPG binding and **increase hemoglobin oxygen affinity**.

Fetal hemoglobin (hemoglobin F) is synthesized primarily during fetal development (~8 weeks until term) and consists of the usual 2 alpha chains with 2 gamma chains in place of beta chains. The gamma chains do not bind effectively to 2,3-BPG due to replacement of a histidine residue with serine. As a result, fetal hemoglobin has significantly higher oxygen affinity than adult hemoglobin A. This allows fetal hemoglobin to extract more oxygen from the mother's adult hemoglobin in the placenta, providing the developing fetus with an adequate supply of oxygen.

(Choice A) Hemoglobin A_{1c} is formed by non-enzymatic glycosylation of hemoglobin A. Glycosylation can interfere with the binding of 2,3-BPG to hemoglobin by altering the physical structure of the binding pocket, which is compensated for by increased red cell 2,3-BPG levels in patients with diabetes. However, the reduced 2,3-BPG binding affinity of this patient's mutated hemoglobin more closely resembles that of hemoglobin F.

(Choice B) Hemoglobin C results from a mutation in the β-globin chain that causes glutamate to be replaced by lysine. Hemoglobin C forms hexagonal crystals and promotes red cell dehydration, causing a mild chronic hemolytic anemia. 2,3-BPG binding and tissue oxygen delivery are not significantly altered.

(Choice D) A defect in the synthesis of alpha chains results in varying degrees of alpha thalassemia, which is characterized by the formation of β-globin and γ-globin tetramers (hemoglobin H and Barts, respectively). These abnormal tetramers have extremely high oxygen affinity (resembling myoglobin) and are ineffective at delivering oxygen to tissues.

(Choice E) Hemoglobin S is the predominant form of hemoglobin in sickle cell disease and is caused by replacement of a glutamate by valine in the β-globin chain. This results in formation of hemoglobin polymers with reduced oxygen affinity.

Educational objective:
2,3-bisphosphoglycerate (2,3-BPG) normally forms ionic bonds with the beta subunits of deoxygenated hemoglobin A, facilitating oxygen release in the peripheral tissues. Mutations that result in loss of the 2,3-BPG binding pocket's positive charge cause hemoglobin A to resemble fetal hemoglobin, which binds oxygen with a higher affinity due to its inability to interact with 2,3-BPG.

Fetal hemoglobin (hemoglobin F) is synthesized primarily during fetal development (~8 weeks until term) and consists of the usual 2 alpha chains with 2 gamma chains in place of beta chains. The gamma chains do not bind effectively to 2,3-BPG due to replacement of a histidine residue with serine. As a result, fetal hemoglobin has significantly higher oxygen affinity than adult hemoglobin A. This allows fetal hemoglobin to extract more oxygen from the mother's adult hemoglobin in the placenta, providing the developing fetus with an adequate supply of oxygen.

(Choice A) Hemoglobin A_{1c} is formed by non-enzymatic glycosylation of hemoglobin A. Glycosylation can interfere with the binding of 2,3-BPG to hemoglobin by altering the physical structure of the binding pocket, which is compensated for by increased red cell 2,3-BPG levels in patients with diabetes. However, the reduced 2,3-BPG binding affinity of this patient's mutated hemoglobin more closely resembles that of hemoglobin F.

(Choice B) Hemoglobin C results from a mutation in the β-globin chain that causes glutamate to be replaced by lysine. Hemoglobin C forms hexagonal crystals and promotes red cell dehydration, causing a mild chronic hemolytic anemia. 2,3-BPG binding and tissue oxygen delivery are not significantly altered.

(Choice D) A defect in the synthesis of alpha chains results in varying degrees of alpha thalassemia, which is characterized by the formation of β-globin and γ-globin tetramers (hemoglobin H and Barts, respectively). These abnormal tetramers have extremely high oxygen affinity (resembling myoglobin) and are ineffective at delivering oxygen to tissues.

(Choice E) Hemoglobin S is the predominant form of hemoglobin in sickle cell disease and is caused by replacement of a glutamate by valine in the β-globin chain. This results in formation of hemoglobin polymers with reduced oxygen affinity.

Educational objective:
2,3-bisphosphoglycerate (2,3-BPG) normally forms ionic bonds with the beta subunits of deoxygenated hemoglobin A, facilitating oxygen release in the peripheral tissues. Mutations that result in loss of the 2,3-BPG binding pocket's positive charge cause hemoglobin A to resemble fetal hemoglobin, which binds oxygen with a higher affinity due to its inability to interact with 2,3-BPG.

Biochemistry	Hematology & Oncology	Hemoglobin properties
Subject	System	Topic

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A 6-year-old African American male is brought to your office for a routine check-up. His mother remarks that he often seems uninterested in playing with his peers and appears to "run out of breath quickly." His medical records reveal that he has missed several pediatric vaccinations and has been hospitalized twice, once with a "chest infection" and once with abdominal pain. The patient mentions to you that occasionally his "bones hurt." Which of the following protein changes most likely accounts for this patient's condition?

A. Phenylalanine deletion

B. Valine substitution for glutamic acid

C. Phenylalanine substitution for proline

D. Valine substitution for lysine

E. Early termination of polypeptide synthesis

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A 6-year-old African American male is brought to your office for a routine check-up. His mother remarks that he often seems uninterested in playing with his peers and appears to "run out of breath quickly." His medical records reveal that he has missed several pediatric vaccinations and has been hospitalized twice, once with a "chest infection" and once with abdominal pain. The patient mentions to you that occasionally his "bones hurt." Which of the following protein changes most likely accounts for this patient's condition?

A. Phenylalanine deletion (2%)
✓ B. Valine substitution for glutamic acid (82%)
C. Phenylalanine substitution for proline (3%)
D. Valine substitution for lysine (9%)
E. Early termination of polypeptide synthesis (2%)

Omitted
Correct answer
B

82%
Answered correctly

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Time Spent

02/03/2020
Last Updated

Explanation

This patient is exhibiting signs and symptoms of sickle cell anemia. Sickle cell anemia is a hemoglobinopathy that typically affects patients of African ancestry. A point mutation in the 6th codon of the beta-globin gene, which causes the substitution of valine (hydrophobic) for glutamic acid (hydrophilic), is responsible. The incorporation of this abnormal beta-globin protein into hemoglobin results in the formation of hemoglobin S (HbS). HbS polymerizes at low oxygen tension, causing sickling and hemolysis of erythrocytes and resultant vascular occlusion. This patient's poor exercise tolerance and exertional dyspnea are due to anemia. His history of acute chest syndrome, abdominal pain, and bone pain are due

Omitted
Correct answer
B

82%
Answered correctly

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02/03/2020
Last Updated

Explanation

This patient is exhibiting signs and symptoms of sickle cell anemia. Sickle cell anemia is a hemoglobinopathy that typically affects patients of African ancestry. A point mutation in the 6th codon of the beta-globin gene, which causes the substitution of valine (hydrophobic) for glutamic acid (hydrophilic), is responsible. The incorporation of this abnormal beta-globin protein into hemoglobin results in the formation of hemoglobin S (HbS). HbS polymerizes at low oxygen tension, causing sickling and hemolysis of erythrocytes and resultant vascular occlusion. This patient's poor exercise tolerance and exertional dyspnea are due to anemia. His history of acute chest syndrome, abdominal pain, and bone pain are due to vaso-occlusive events in the lungs, spleen and bone, respectively.

(Choice A) A phenylalanine deletion (ΔF508) is the most common cause of cystic fibrosis, the most common fatal genetic disease of Caucasians.

(Choice E) Early termination of polypeptide synthesis (nonsense mutation) will produce a truncated protein.

Educational Objective:
Exertional dyspnea, pneumonia resulting in life-threatening acute chest syndrome, and recurrent abdominal and bone pain are clinical features of sickle cell anemia. Sickle cell anemia results from a point mutation that causes valine to substitute for glutamic acid in the sixth position of the b-globin chain of hemoglobin.

Biochemistry	Hematology & Oncology	Sickle cell
Subject	System	Topic

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A 79-year-old woman comes to the office for evaluation of difficulty walking due to fatigue and bilateral leg pain. The pain started in her lower legs 3 weeks ago and progressed to involve the muscles of her thighs also. In addition, she has noted red spots on her legs. The patient has lived alone since her husband died 3 years ago and is largely homebound. Her diet consists mostly of bread and canned meat products. On examination, the gums are swollen and tender. The patient's skin findings are shown in the exhibit. Muscles of the lower limbs are tender to palpation. Imaging studies reveal a tibial subperiosteal hematoma. Which of the following nutrient deficiencies is most likely responsible for this patient's symptoms?

- A. Ascorbic acid
- B. Biotin
- C. Folic acid
- D. Linoleic acid
- E. Pyridoxine
- F. Riboflavin
- G. Thiamine
- H. Vitamin K
- I. Zinc

Submit

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- ✓ A. Ascorbic acid (77%)
- B. Biotin (0%)
- C. Folic acid (2%)
- D. Linoleic acid (0%)
- E. Pyridoxine (1%)
- F. Riboflavin (1%)
- G. Thiamine (1%)
- H. Vitamin K (12%)
- I. Zinc (1%)

Omitted
Correct answer
A

77%
Answered correctly

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Last Updated

This patient with perifollicular hemorrhages, myalgias, subperiosteal hematoma, and gingivitis has typical features of **scurvy**. Scurvy, which is due to a deficiency of **ascorbic acid** (vitamin C), is uncommon in developed countries as this vitamin is widely available in fruits, vegetables, and a variety of other foods. However, it may occasionally be seen in patients with abnormal eating patterns, including the elderly, alcoholics, and persons who live alone. Other possible signs of scurvy include hemarthrosis, **petechial hemorrhages**, impaired wound healing, and weakened immune responses to local infections.

Ascorbic acid is a cofactor in a number of reactions but is especially important in the hydroxylation of proline and lysine residues. In particular, synthesis of **collagen** requires extensive formation of **hydroxyproline** in the procollagen polypeptide, and ascorbic acid deficiency leads to reduced production of collagen with lower tensile strength. Collagen defects in blood vessel walls lead to widespread microvascular bleeding.

(Choice B) Biotin plays a role in a number of carboxylation reactions. Deficiency is rare but can present with rash, hair loss, and neuropsychiatric defects.

(Choice C) Folic acid deficiency is characterized by megaloblastic anemia and fetal neural tube defects.

(Choice D) Linoleic acid is an essential fatty acid used in the synthesis of arachidonic acid. Deficiency is not well characterized, but reported features include growth deficiency and neurovisual defects.

(Choice E) Pyridoxine (vitamin B_6) deficiency is characterized by cheilosis, glossitis, dermatitis, and peripheral neuropathy.

(Choice F) Vitamin B_2 (riboflavin) deficiency is characterized by angular stomatitis, cheilitis, glossitis, seborrheic dermatitis, eye changes (eg, keratitis, corneal neovascularization), and anemia.

(Choice G) Vitamin B_1 (thiamine) deficiency causes beriberi (peripheral neuropathy, muscle wasting, and heart failure), Wernicke syndrome (nystagmus, ataxia, and ophthalmoplegia), and Korsakoff psychosis.

(Choice H) Vitamin K deficiency is characterized by a bleeding diathesis (but not painful gums).

(Choice I) Zinc deficiency is characterized by acrodermatitis enteropathica, growth retardation, and infertility.

Educational objective:
Ascorbic acid (vitamin C) is a cofactor in the hydroxylation of proline and lysine residues and is important in the synthesis of collagen. Deficiency (scurvy) is characterized by microvascular bleeding, gingivitis, and impaired wound healing.

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Ascorbic acid is a cofactor in a number of reactions but is especially important in the hydroxylation of proline and lysine residues. In particular,

Exhibit Display

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A researcher is studying the role of glucose metabolites in normal cellular function. A specific human cell type is incubated in glucose-rich media. Intracellular levels of glucose metabolizing enzymes, intermediate products, and generated ATP are measured. In these cells, glycolysis of a single glucose molecule always yields pyruvate but sometimes generates no net ATP. Which of the following cells is most likely being studied in this experiment?

A. Adipocytes
B. Erythrocytes
C. Hepatocytes
D. Neurons
E. Skeletal muscle cells

Submit

A researcher is studying the role of glucose metabolites in normal cellular function. A specific human cell type is incubated in glucose-rich media. Intracellular levels of glucose metabolizing enzymes, intermediate products, and generated ATP are measured. In these cells, glycolysis of a single glucose molecule always yields pyruvate but sometimes generates no net ATP. Which of the following cells is most likely being studied in this experiment?

- A. Adipocytes (8%)
- ✓ B. Erythrocytes (70%)
- C. Hepatocytes (8%)
- D. Neurons (2%)
- E. Skeletal muscle cells (9%)

Omitted
Correct answer
B

70%
Answered correctly

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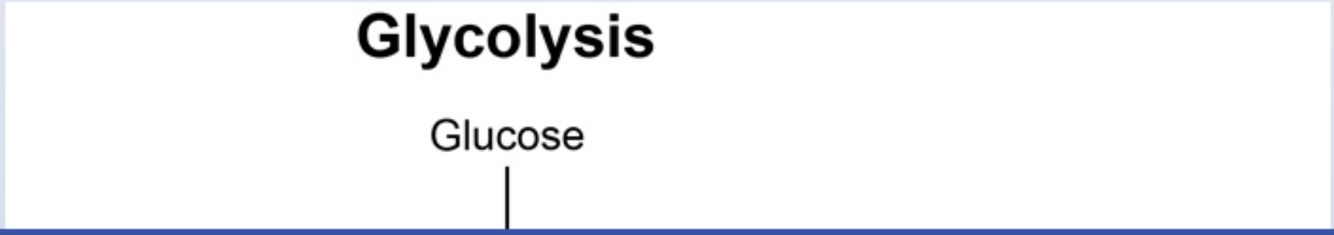
Time Spent

03/16/2020
Last Updated

Explanation



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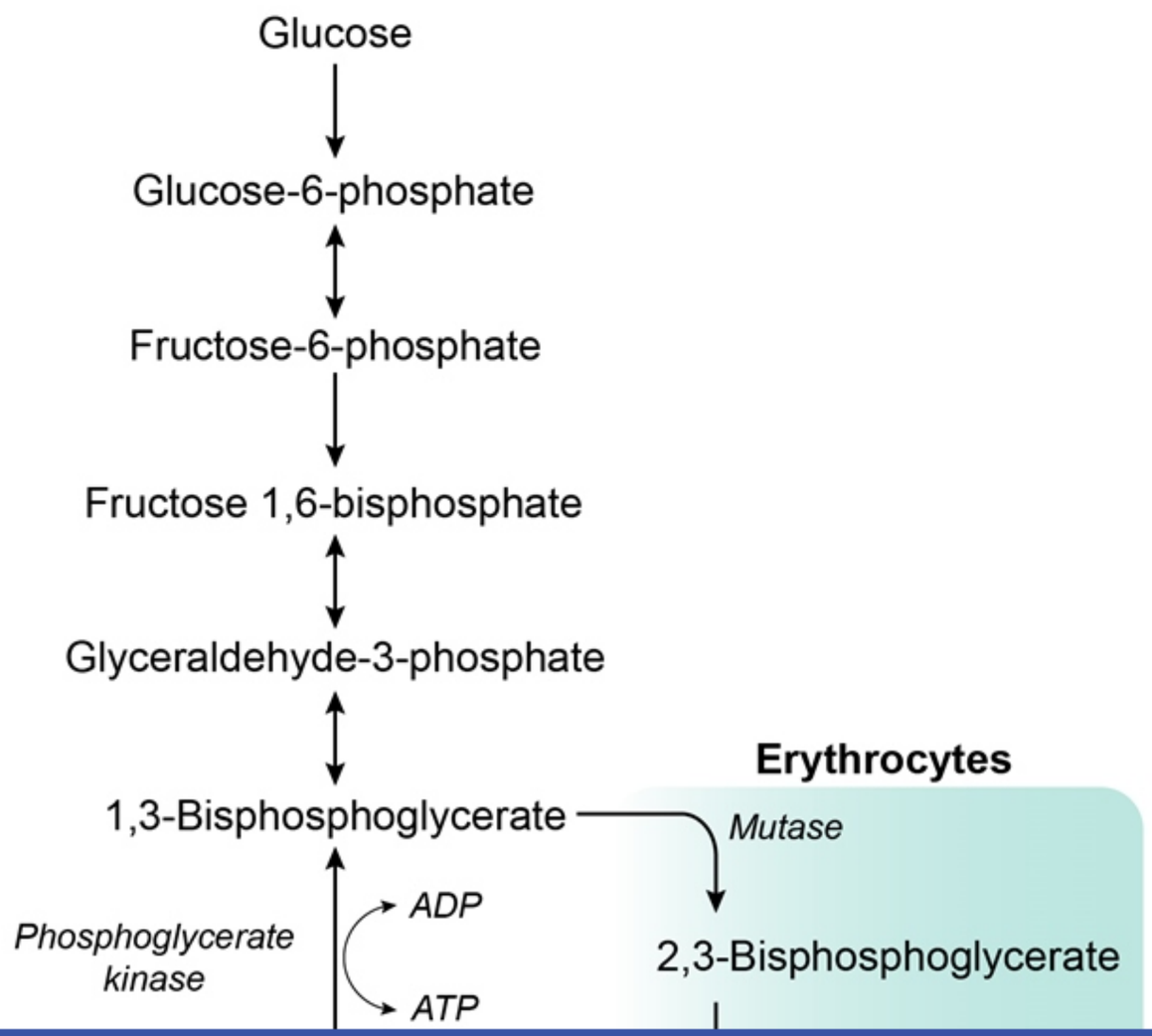
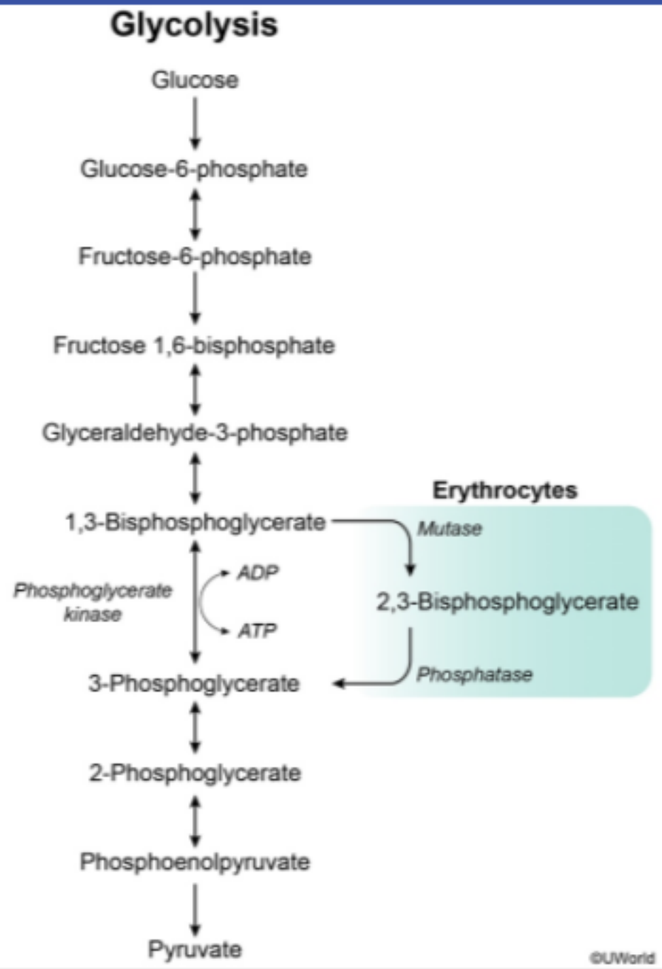
Glycolysis



Glucose-6-phosphate

Exhibit Display



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Erythrocytes use glycolysis as the major pathway to generate energy as they do not have mitochondria and therefore cannot use the citric acid cycle. During normal glycolysis, ATP is generated when 1,3-BPG is converted to 3-phosphoglycerate by the enzyme phosphoglycerate kinase. However, erythrocytes can bypass this part of the pathway using **bisphosphoglycerate mutase**, an enzyme that converts 1,3-BPG to **2,3-BPG** in a step that produces **no ATP**. 2,3-BPG is subsequently catabolized to 3-phosphoglycerate by bisphosphoglycerate phosphatase in a step that also yields no ATP. By generating 2,3-BPG rather than proceeding with regular glycolysis, erythrocytes sacrifice the net ATP gain achieved in normal glycolysis.

The major function of erythrocytes is to carry hemoglobin-bound oxygen from the lungs to the peripheral tissues, and 2,3-BPG is a very important regulator of oxygen-hemoglobin binding. The conversion of 1,3-BPG to 2,3-BPG is increased in **hypoxia** and chronic anemia. 2,3-BPG allosterically decreases hemoglobin's affinity for oxygen. As a result, in the presence of lower blood oxygen concentrations, higher 2,3-BPG levels within erythrocytes enable **increased oxygen delivery** in the peripheral tissues.

(Choices A, C, D, and E) The enzyme bisphosphoglycerate mutase is present in large amounts in erythrocytes. However, it is present in insignificant quantities in adipocytes, hepatocytes, neurons, and myocytes; this causes virtually negligible 2,3-BPG production in these cell types.

Educational objective:
2,3-BPG decreases hemoglobin's affinity for oxygen. Therefore, in the presence of lower blood oxygen concentrations, higher 2,3-BPG levels within erythrocytes enable increased oxygen delivery in the peripheral tissues. 2,3-BPG is produced from 1,3-BPG by the enzyme bisphosphoglycerate mutase. This reaction bypasses an ATP-generating step of glycolysis, causing no net gain in ATP.

References

- Dephosphorylation of 2,3-bisphosphoglycerate by MIPP expands the regulatory capacity of the Rapoport-Luebering glycolytic shunt.
- The energy-less red blood cell is lost: erythrocyte enzyme abnormalities of glycolysis.

Biochemistry	Hematology & Oncology	Glycolysis
Subject	System	Topic

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A 34-year-old industry worker experiences rapid-onset shortness of breath, dizziness, palpitations, and flushed skin after accidental exposure to chemical fumes. Examination by an occupational physician shows that the patient is tachypneic and has a reddish discoloration of the skin without cyanosis. The patient is immediately instructed to inhale amyl nitrite from the safety kit. The success of this antidote is dependent upon its ability to convert hemoglobin into a form with increased affinity for which of the following substances?

A. 2,3-biphosphoglycerate
B. Carbon dioxide
C. Carbon monoxide
D. Cyanide
E. Iron
F. Lead

Submit

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- A. 2,3-biphosphoglycerate (23%)
- B. Carbon dioxide (9%)
- C. Carbon monoxide (8%)
- ✓ D. Cyanide (50%)
- E. Iron (6%)
- F. Lead (0%)

Omitted
Correct answer
D

50%
Answered correctly

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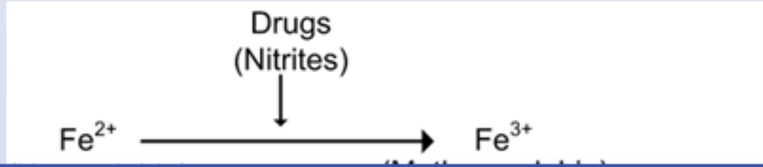
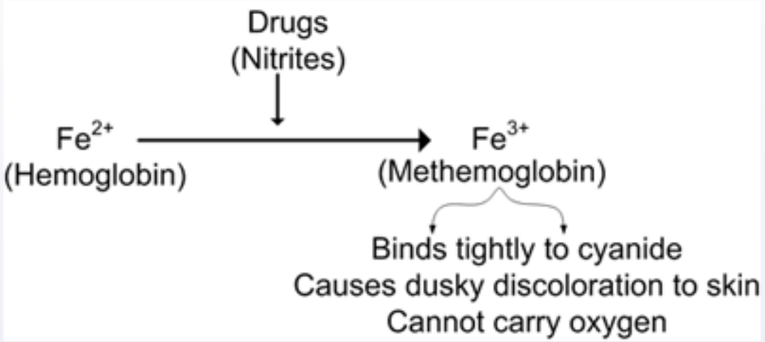
Time Spent

05/13/2020
Last Updated

Explanation





The toxicity of **cyanide** is dependent upon its ability to bind **ferric iron** (Fe^{3+}) with high affinity, inhibiting **cytochrome c oxidase** in the mitochondria. This electron transport chain enzyme is essential for oxidative phosphorylation; inhibition results in severe lactic acidosis and death as a result of cells switching to anaerobic metabolism.

Cyanide poisoning presents with **reddish skin discoloration**, tachypnea, headache, and tachycardia, often accompanied by nausea/vomiting, confusion, and weakness. Symptoms develop rapidly and can quickly progress to seizures and cardiovascular collapse. Laboratory studies indicate severe **lactic acidosis** in conjunction with a **narrowing of the venous-arterial PO_2 gradient**, resulting from the inability of tissue to extract arterial oxygen.

Administration of **inhaled amyl nitrite** oxidizes ferrous iron (Fe^{2+}) present in hemoglobin to ferric iron (Fe^{3+}), generating **methemoglobin**. Methemoglobin is incapable of carrying oxygen but has a high affinity for cyanide; it binds and sequesters cyanide in the blood, freeing it from cytochrome oxidase and limiting its toxic effects. Hydroxycobalamin, a vitamin B_{12} precursor, and sodium thiosulfate are also antidotes for cyanide poisoning. Their interactions with cyanide generate relatively nontoxic metabolites that are easily excreted in the urine.

(Choices A and B) The presence of 2,3-biphosphoglycerate causes a right shift in the oxygen-hemoglobin dissociation curve, decreasing hemoglobin's affinity for oxygen and increasing its affinity for carbon dioxide.

(Choice C) Hemoglobin has a much higher affinity for carbon monoxide than it does for oxygen. This is the basis for carbon monoxide poisoning, which is treated with high-flow oxygen.

(Choice E) The affinity of hemoglobin for iron is not affected by nitrite administration, although nitrites do oxidize the heme iron to its Fe^{3+} state.

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Cyanide poisoning presents with **reddish skin discoloration**, tachypnea, headache, and tachycardia, often accompanied by nausea/vomiting, confusion, and weakness. Symptoms develop rapidly and can quickly progress to seizures and cardiovascular collapse. Laboratory studies indicate severe **lactic acidosis** in conjunction with a **narrowing of the venous-arterial PO_2 gradient**, resulting from the inability of tissue to extract arterial oxygen.

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(Choice F) Lead poisoning causes defective heme synthesis. If lead is acutely ingested, chelation therapy with dimercaprol or edetate disodium calcium ($CaNa_2EDTA$) should be initiated.

Educational objective:
Nitrites are oxidizing agents that are effective in treating cyanide poisoning due to their ability to induce methemoglobinemia. Methemoglobin contains ferric (Fe^{3+}) rather than ferrous iron (Fe^{2+}). Cyanide binds to ferric iron more avidly than to mitochondrial cytochrome enzymes, diminishing cyanide's toxic effect.

Biochemistry	Hematology & Oncology	Cyanide poisoning
Subject	System	Topic

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A 52-year-old woman comes to the office with a 2-month history of skin rash that worsens with sun exposure. Her family says that lately she has become irritable, hostile, and has had episodes of disorientation. The patient does not use tobacco or illicit drugs but has been drinking half a bottle of gin daily. Further questioning reveals poor nutritional intake and intermittent diarrhea. The patient restricts her diet for weight control. Body mass index is 17 kg/m^2. On examination, she has a well-demarcated, hyperpigmented, scaly rash on the hands, forearms, and upper chest. The cause of most of her symptoms is determined to be a lack of the precursor vitamin for synthesis of NAD$^+$ coenzyme. The compensatory pathway to synthesize this coenzyme uses which of the following as a precursor?

A. Arginine
B. Carotene
C. Cholesterol
D. Orotic acid
E. Phenylalanine
F. Tryptophan

Submit

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- A. Arginine (15%)
- B. Carotene (5%)
- C. Cholesterol (3%)
- D. Orotic acid (7%)
- E. Phenylalanine (7%)
- ✓ F. Tryptophan (60%)

Omitted
Correct answer
F

60%
Answered correctly

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01/08/2020
Last Updated

Explanation

Niacin metabolism

Diet

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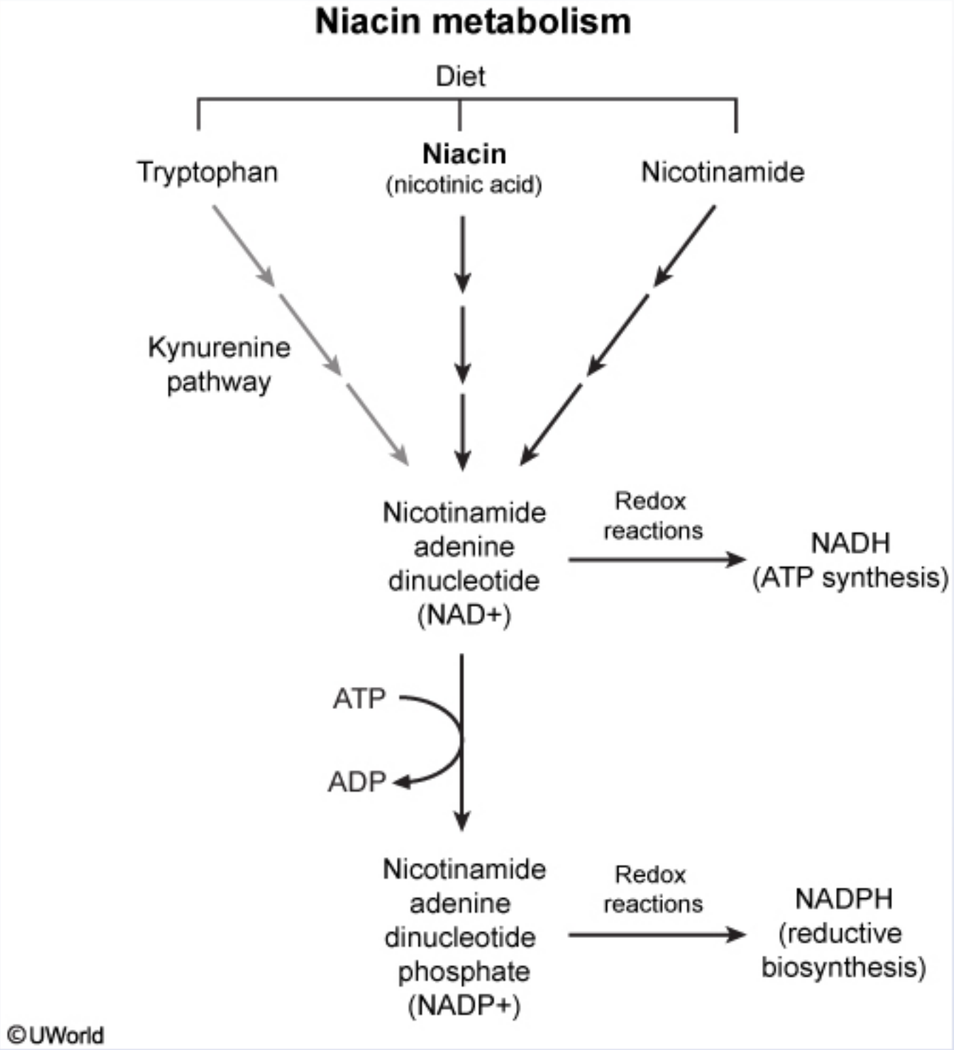

Pellagra ("rough skin" in Italian vernacular) is due to **niacin deficiency** and is characterized by the "3 Ds": **dermatitis, diarrhea, and dementia**:

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Pellagra ("rough skin" in Italian vernacular) is due to **niacin deficiency** and is characterized by the "3 Ds": **dermatitis, diarrhea, and dementia**:

- Dermatitis is bilateral and symmetric on sun-exposed areas of the body and is characterized by rough, thick, scaly skin.
- Diarrhea is due to atrophy (and occasional ulceration) of columnar epithelium of the gastrointestinal tract.
- Dementia is due to neuronal degeneration in the brain and spinal cord, with lesions similar to those associated with pernicious anemia.

Niacin (nicotinic acid, or vitamin B_3) is an essential component of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which participate in redox metabolism. Specifically, NAD functions as a coenzyme for dehydrogenases involved in the metabolism of fats, carbohydrates, and amino acids; NADP is crucial in the hexose-monophosphate shunt of glucose metabolism and for biosynthesis of cholesterol and fatty acids.

Niacin can be obtained through dietary intake or **synthesized endogenously** from **tryptophan**. In developing countries, niacin deficiency is seen in populations that subsist primarily on corn products (niacin in corn occurs in a bound, unabsorbable form). In developed countries, it is primarily seen in patients with impaired nutritional intake (eg, alcoholism, chronic illness). Pellagra can also be seen occasionally in those with carcinoid syndrome, prolonged isoniazid therapy, or Hartnup disease.

(Choice A) Arginine is the precursor of nitric oxide, urea, ornithine, and agmatine. It is also necessary for the formation of creatine.

(Choice B) Carotene is the precursor to vitamin A.

(Choice C) Cholesterol is the precursor to steroid hormones.

(Choice D) Orotic acid is a precursor of pyrimidine.

(Choice E) Phenylalanine is the precursor to tyrosine, an amino acid necessary for the formation of catecholamines.

Educational objective:
Niacin (vitamin B_3) can be synthesized endogenously from tryptophan and is an essential component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). A deficiency of this vitamin results in pellagra, which is characterized by dermatitis, diarrhea, and dementia.

References

adenine dinucleotide phosphate (NADP), which participate in redox metabolism. Specifically, NAD functions as a coenzyme for dehydrogenases involved in the metabolism of fats, carbohydrates, and amino acids; NADP is crucial in the hexose-monophosphate shunt of glucose metabolism and for biosynthesis of cholesterol and fatty acids.

Niacin can be obtained through dietary intake or **synthesized endogenously** from **tryptophan**. In developing countries, niacin deficiency is seen in populations that subsist primarily on corn products (niacin in corn occurs in a bound, unabsorbable form). In developed countries, it is primarily seen in patients with impaired nutritional intake (eg, alcoholism, chronic illness). Pellagra can also be seen occasionally in those with carcinoid syndrome, prolonged isoniazid therapy, or Hartnup disease.

(Choice A) Arginine is the precursor of nitric oxide, urea, ornithine, and agmatine. It is also necessary for the formation of creatine.

(Choice B) Carotene is the precursor to vitamin A.

(Choice C) Cholesterol is the precursor to steroid hormones.

(Choice D) Orotic acid is a precursor of pyrimidine.

(Choice E) Phenylalanine is the precursor to tyrosine, an amino acid necessary for the formation of catecholamines.

Educational objective:
Niacin (vitamin B_3) can be synthesized endogenously from tryptophan and is an essential component of nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). A deficiency of this vitamin results in pellagra, which is characterized by dermatitis, diarrhea, and dementia.

References

- Pellagra and alcoholism: a biochemical perspective.

Biochemistry	Dermatology	Niacin deficiency
Subject	System	Topic

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In an experiment, erythrocyte precursor cells are incubated in a medium containing radiolabeled cysteine. These radiolabeled cysteine residues are attached to their appropriate tRNAs by the enzyme aminoacyl-tRNA synthetase. The bound cysteine residues are then chemically modified to form alanine. The end product of this reaction is a tRNA molecule that contains the cysteine anticodon but is mischarged with alanine. Which of the following is most likely to occur to this alanine residue during polypeptide synthesis of alpha-hemoglobin?

A. It will be incorporated into the polypeptide chain at a site requiring alanine

B. It will be incorporated into the polypeptide chain at a site requiring cysteine

C. It will be randomly incorporated into the polypeptide chain, halting chain elongation

D. It will be rapidly cleaved off tRNA by the enzyme glycosylase

E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA

Submit

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- A. It will be incorporated into the polypeptide chain at a site requiring alanine (5%)
- ✓ B. It will be incorporated into the polypeptide chain at a site requiring cysteine (69%)
- C. It will be randomly incorporated into the polypeptide chain, halting chain elongation (5%)
- D. It will be rapidly cleaved off tRNA by the enzyme glycosylase (13%)
- E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA (6%)

Omitted
Correct answer
B

69%
Answered correctly

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Last Updated

Explanation

Amino acid activation and attachment to the 3' end of tRNA are catalyzed by **aminoacyl-tRNA synthetases** (AA-tRNA synthetases). Each amino acid/tRNA pair has a specific AA-tRNA synthetase that links them together. These enzymes are responsible for ensuring that each amino acid binds to the tRNA with the proper anticodon. AA-tRNA synthetase activation and binding sites are **highly specific** for their correct amino acids and tRNA molecules. In addition, some AA-tRNA synthetases can **"proofread"** their specific tRNA molecules and hydrolyze the amino acid bond when their tRNAs are incorrectly charged. The error rate for AA-tRNA synthetases is therefore very low, with less than 1 error per 10^4 charges.

Amino acid activation and attachment to the 3' end of tRNA are catalyzed by **aminoacyl-tRNA synthetases** (AA-tRNA synthetases). Each amino acid/tRNA pair has a specific AA-tRNA synthetase that links them together. These enzymes are responsible for ensuring that each amino acid binds to the tRNA with the proper anticodon. AA-tRNA synthetase activation and binding sites are **highly specific** for their correct amino acids and tRNA molecules. In addition, some AA-tRNA synthetases can **"proofread"** their specific tRNA molecules and hydrolyze the amino acid bond when their tRNAs are incorrectly charged. The error rate for AA-tRNA synthetases is therefore very low, with less than 1 error per 10^4 charges.

During protein synthesis, tRNA acts as an adaptor molecule between the codons found on mRNA and the amino acids being incorporated into the polypeptide chain. The amino acid sequence in a polypeptide chain is dictated by the binding of a tRNA anticodon to its complementary codon on the mRNA molecule being translated. **Erroneous amino acid/tRNA coupling** by AA-tRNA synthetase causes the **wrong amino acid** to be **incorporated** into the growing polypeptide chain **(Choice E)**.

For example, under normal circumstances, when the ribosome encounters a cysteine codon (eg, UGU) on mRNA, the complementary tRNA anticodon (eg, ACA) binds. If this tRNA is improperly charged with alanine, as described in the experiment above, alanine will be incorrectly incorporated into the growing polypeptide chain in place of cysteine **(Choice A)**.

(Choice C) During polypeptide chain elongation, ribosomes move from codon to codon on mRNA in the 5' to 3' direction, sequentially adding amino acids from aminoacyl-tRNA to the peptide chain. This continues until the ribosome encounters a stop codon (ie, UAA, UAG, or UGA). Releasing factors then assist in polypeptide chain termination.

(Choice D) DNA glycosylases are enzymes involved in DNA base excision repair.

Educational objective:
The sequence of amino acids in a growing polypeptide chain is dictated by the interaction of the mRNA codon with the tRNA anticodon. tRNA that is mischarged with the incorrect amino acid (and not corrected by aminoacyl-tRNA synthetase proofreading) will incorporate the wrong amino acid into the growing polypeptide chain.

References

- Quality control in aminoacyl-tRNA synthesis its role in translational fidelity.

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A group of investigators is researching the changes in oxygen-hemoglobin binding that occur under various clinical conditions. They are especially interested in situations that alter the shape and position of the oxygen-hemoglobin dissociation curve. Which of the following processes would most likely cause a shift from the blue curve to the red curve in the graph below?

A. Chronic high-altitude adaptation
B. Hypothermia
C. Hypoventilation
D. Severe anemia
E. Strenuous exercise

Submit

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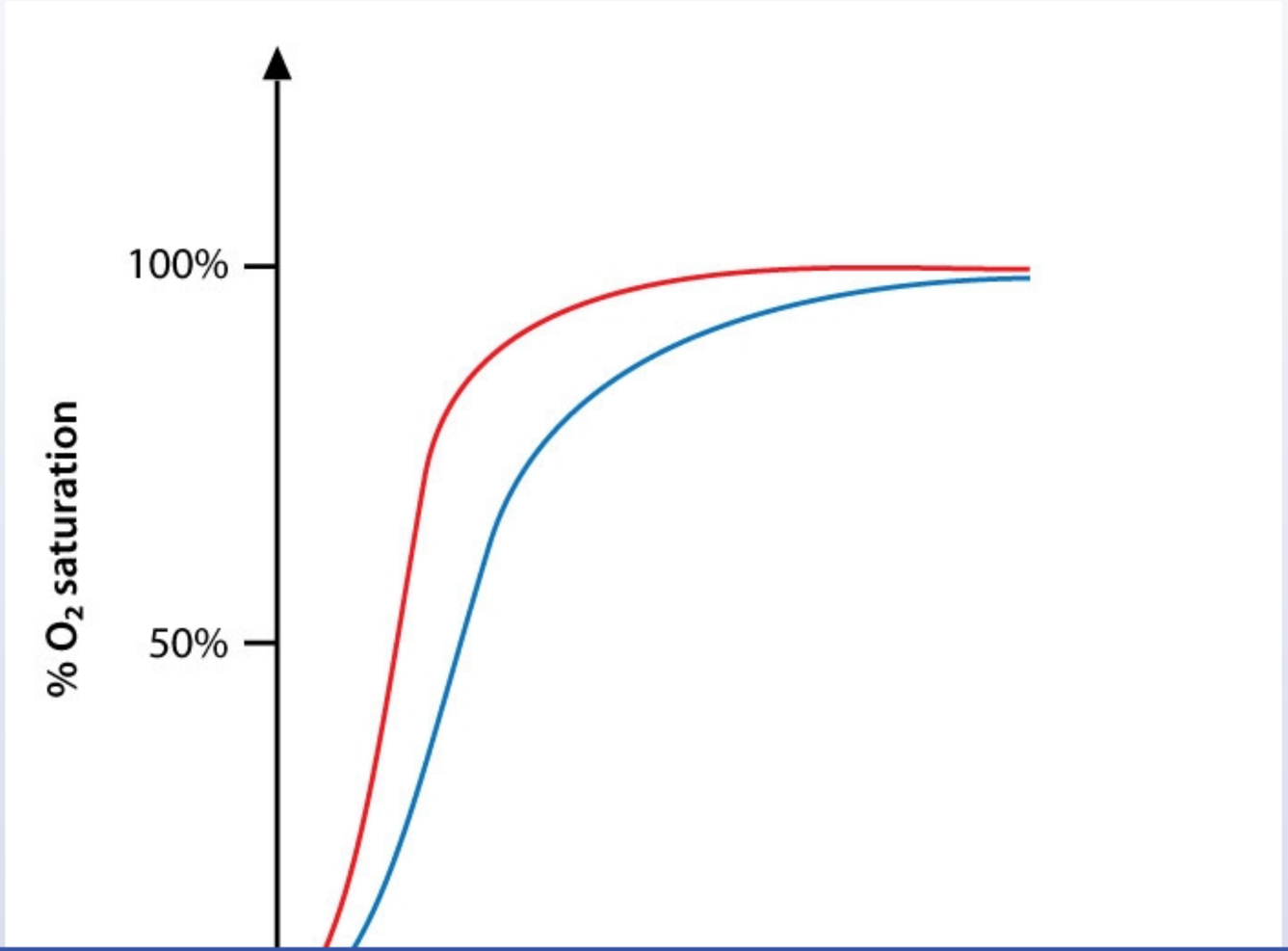

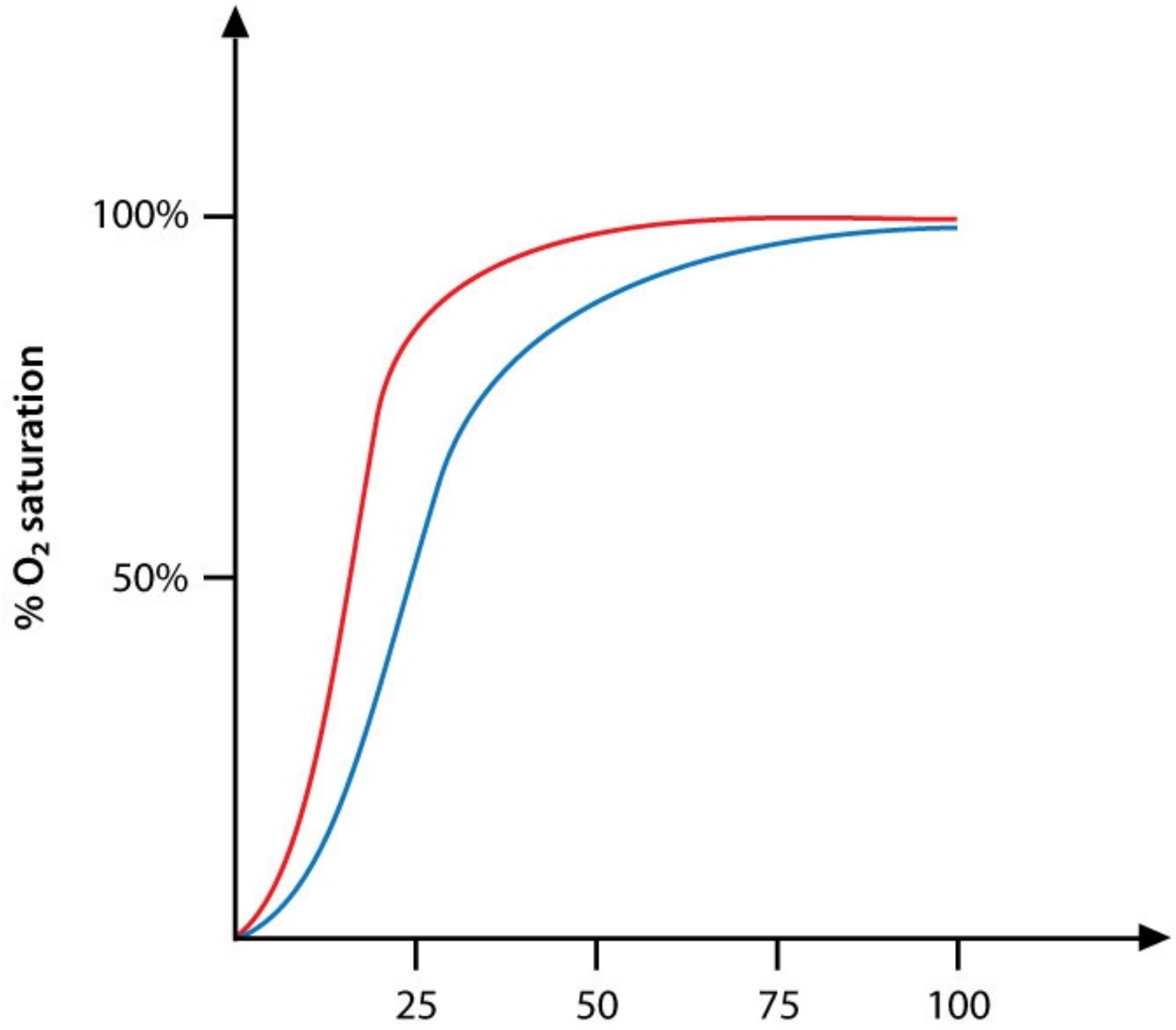
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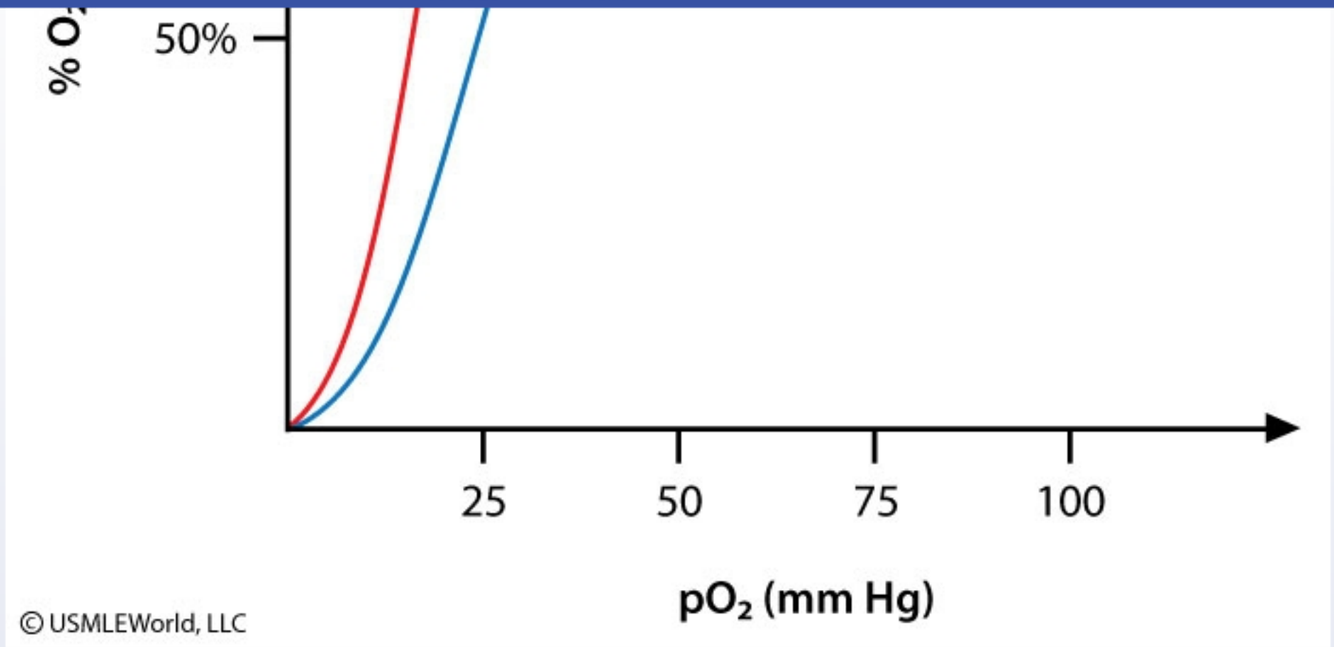

A. Chronic high-altitude adaptation
B. Hypothermia
C. Hypoventilation
D. Severe anemia
E. Strenuous exercise

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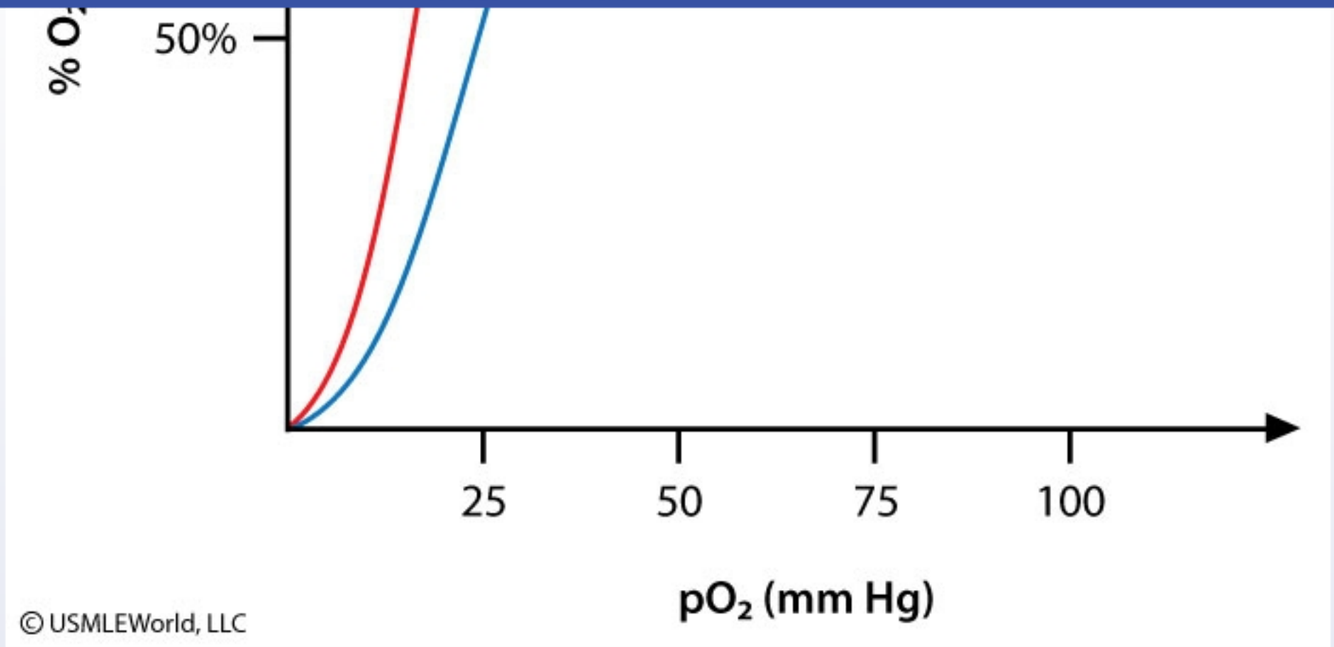

A. Chronic high-altitude adaptation (20%)
✓ B. Hypothermia (61%)
C. Hypoventilation (5%)
D. Severe anemia (5%)
E. Strenuous exercise (7%)

Omitted
Correct answer

61%
Answered correctly

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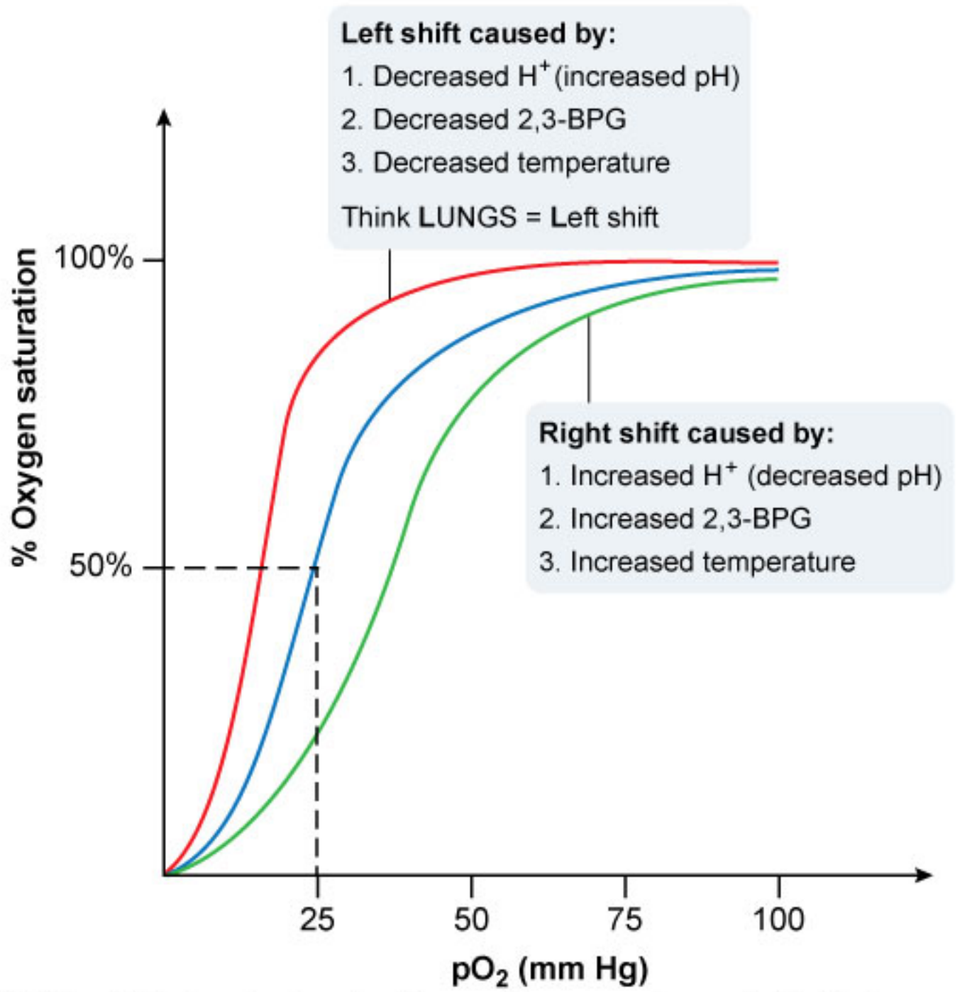
Oxygen-hemoglobin dissociation curve



2,3-BPG = 2,3-bisphosphoglycerate; **pO_2** = partial pressure of oxygen in the blood.

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The oxygen-hemoglobin dissociation curve describes the relationship between the partial pressure of oxygen (x-axis) and the hemoglobin oxygen saturation (y-axis). Oxygen saturation increases in a sigmoidal fashion as the pO_2 increases because of the increase in oxygen-binding affinity that occurs after the first oxygen molecule binds to hemoglobin. As more oxygen molecules bind to hemoglobin, the number of available binding sites decreases and the curve eventually flattens out.

The partial pressure of oxygen in the blood at which hemoglobin is 50% saturated is known as the P_{50} (dotted black line in diagram above); this value is a standard measure of hemoglobin's affinity for oxygen and is about 26 mm Hg in normal individuals. A **leftward shift** of the oxygen-hemoglobin dissociation curve occurs when hemoglobin has **increased oxygen affinity** (ie, a lower P_{50}). Because decreased temperatures help to stabilize the bonds between oxygen and hemoglobin, **hypothermia** increases hemoglobin's oxygen affinity and shifts the dissociation curve to the left.

(Choice A) 2,3-bisphosphoglycerate (2,3-BPG) concentrations increase in erythrocytes when oxygen availability is reduced, as occurs in chronic lung disease, heart failure, and chronic exposure to high altitudes. Elevated levels of 2,3-BPG decrease hemoglobin O_2 affinity (right-shifted curve), allowing release of additional O_2 in the peripheral tissues.

(Choices C and D) Anemia severe enough to cause lactic acidosis will result in lower blood pH, shifting the hemoglobin curve to the right. Similarly, hypoventilation causes increased CO_2 retention and respiratory acidosis that shifts the curve to the right.

(Choice E) Strenuous exercise will cause increased tissue oxidative phosphorylation, increased tissue CO_2 levels, and decreased tissue pH. This results in a shift of the dissociation curve to the right and decreased hemoglobin O_2 affinity.

Educational objective:
A left shift of the hemoglobin oxygen dissociation curve indicates increased hemoglobin O_2 affinity and can be caused by increased pH, decreased 2,3-bisphosphoglycerate, and decreased temperature. Leftward shifts of the curve inhibit the release of O_2 within peripheral tissues.

Biochemistry	Hematology & Oncology	Hemoglobin properties
Subject	System	Topic

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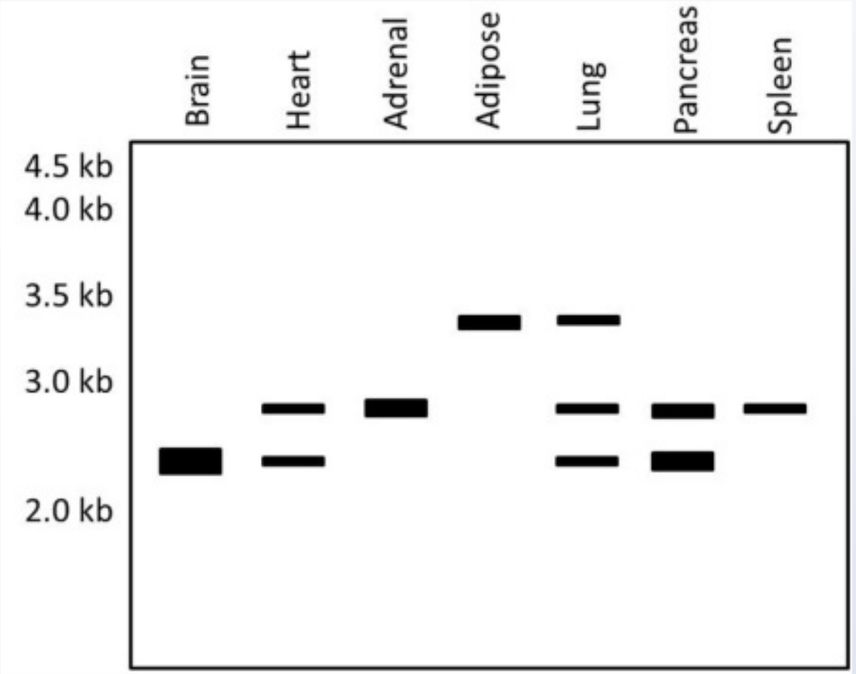
A researcher is studying the expression pattern of a particular gene. Messenger RNA is isolated from several tissues, subjected to electrophoresis, blotted, and probed with radiolabeled DNA containing sequences from exon 4 from that gene. An x-ray film is then placed over the blotting membrane, with the results of the autoradiogram shown below:



Which of the following best explains the autoradiogram findings in the different tissues?

A. Alternate RNA splicing

B. DNA rearrangement

C. DNA mutation

D. Enhancer effect

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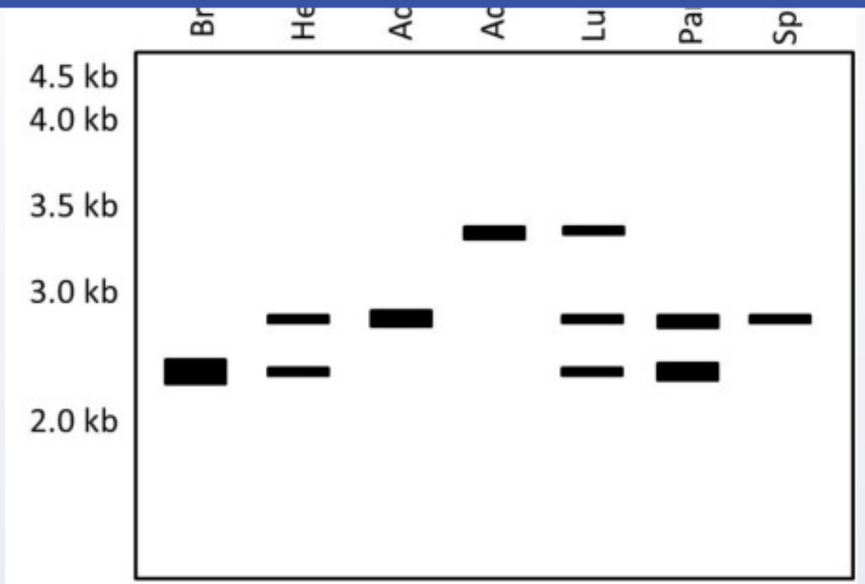

Which of the following best explains the autoradiogram findings in the different tissues?

- A. Alternate RNA splicing
- B. DNA rearrangement
- C. DNA mutation
- D. Enhancer effect
- E. Transcription factor effect

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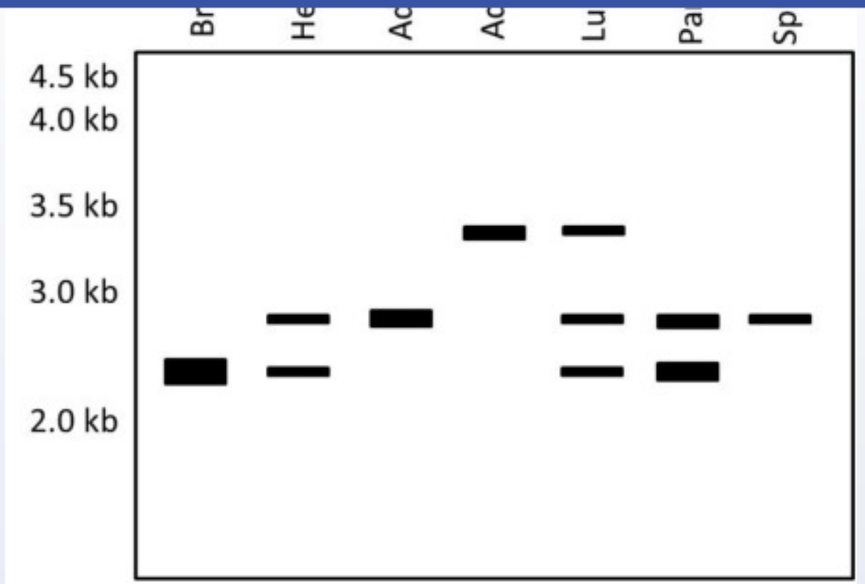

Which of the following best explains the autoradiogram findings in the different tissues?

- A. Alternate RNA splicing (78%)
- B. DNA rearrangement (4%)
- C. DNA mutation (2%)
- D. Enhancer effect (4%)
- E. Transcription factor effect (10%)

Omitted
Correct answer

78%
Answered correctly

04 secs
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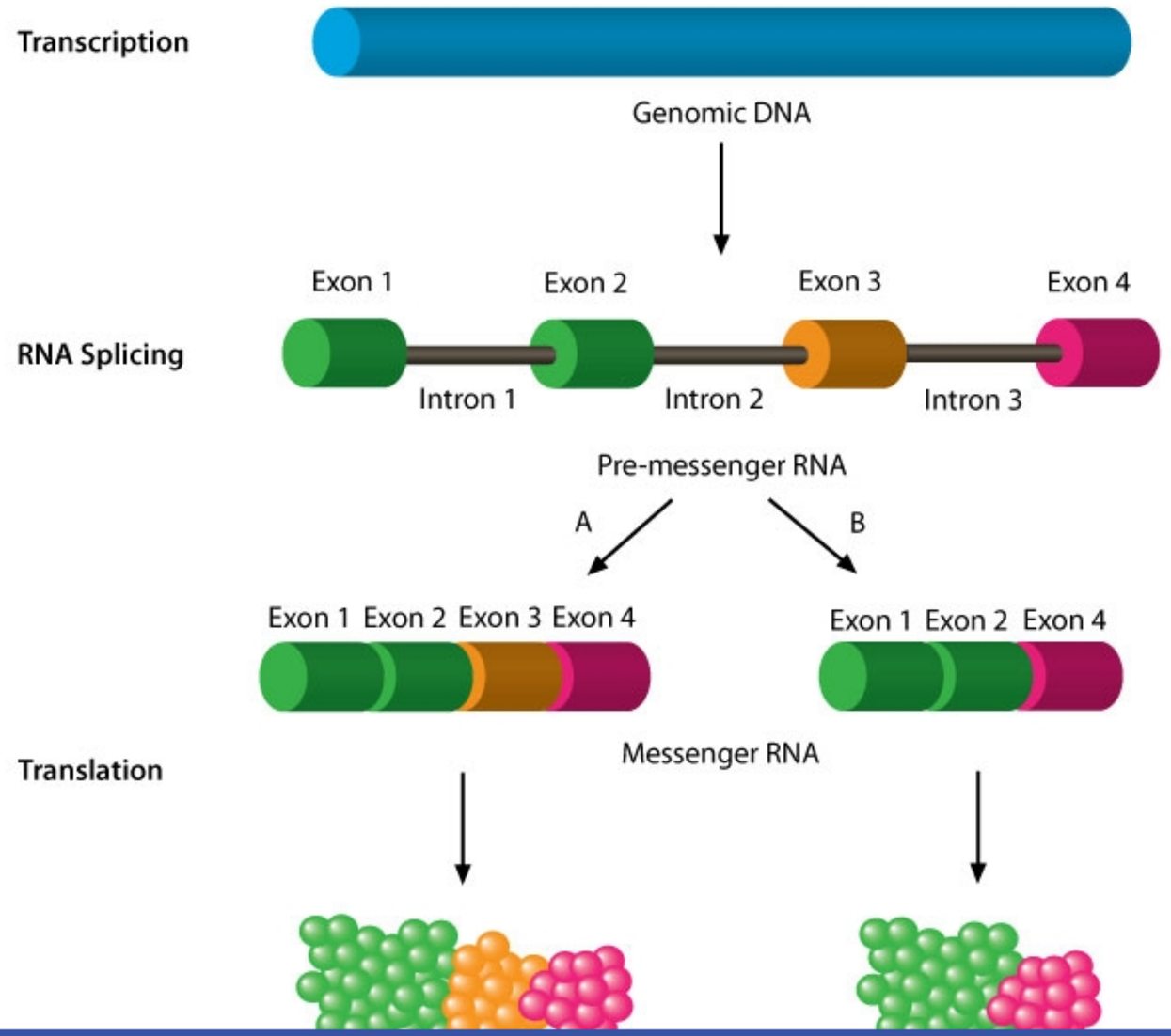

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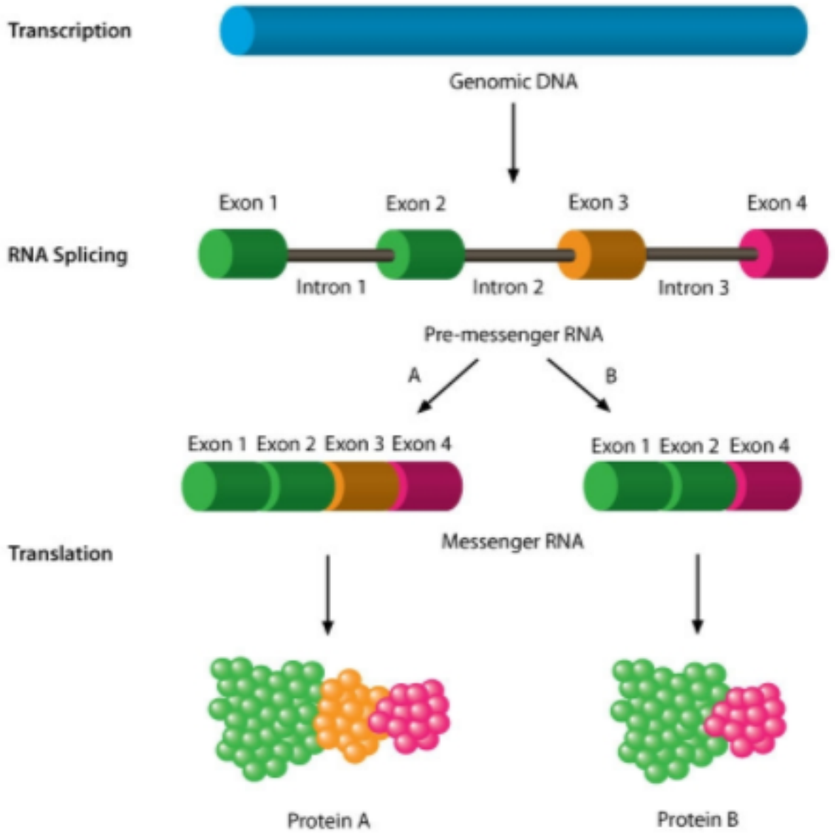

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The experiment described above is known as the Northern Blot technique, a procedure used to detect specific mRNA sequences in a sample to assess for gene expression. In this experiment, the Northern Blot identifies three different mRNA transcripts containing exon 4, with varying patterns of expression in the different tissues. This is consistent with alternative splicing, a process whereby the exons of the pre-mRNA produced by transcription of a gene are reconnected in multiple ways during post-transcriptional processing. The resulting finalized mRNAs are then translated into different protein isoforms. Thus, a single gene can code for multiple proteins when the same gene is spliced differently in different tissues.

Alternative splicing is a normal phenomenon in eukaryotes that greatly increases the biodiversity of proteins that can be encoded by the genome. It is thought that at least 70% of the 30,000 genes in the human genome undergo alternative splicing, and that on average, a given gene produces 4 alternatively spliced variants. Thus, the human genome is able to encode a total of 80,000 to 100,000 proteins which differ in their sequence and function.

Abnormal variations in splicing are implicated in many diseases (e.g., beta-thalassemia, cancer). Alternative splicing also plays a prominent role in the lifecycle of many retroviruses. For instance, HIV produces a single primary RNA transcript that is alternatively spliced to produce over 40 different mRNAs.

(Choice B) DNA (gene) rearrangement occurs during the development and maturation of B cells and T cells. VDJ (**V**ariable, **D**iverse, and **J**oining) gene recombination is a random process that takes place in the primary lymphoid tissue (the bone marrow for B cells, and Thymus for T cells).

(Choice C) A mutation is a change in the DNA sequence of a gene. While somatic mutations do sporadically occur throughout the body, they do so only in a minority of cells. The vast majority of DNA throughout the body's tissues consists of identical gene coding sequences.

(Choice D & E) Transcription factors influence RNA polymerase's affinity for specific genes by binding to DNA promoter sequences or enhancer regions, which can either stimulate or inhibit gene transcription. Transcription factors and enhancer regions affect the expression of pre-mRNA, but they do not influence post-transcriptional processing.

Educational objective:
Alternative splicing is a process where the exons of a gene are reconnected in multiple ways during post-transcriptional processing. This creates different mRNA sequences and subsequently, different protein isoforms. It is a normal phenomenon in eukaryotes that greatly increases the

4 alternatively spliced variants. Thus, the human genome is able to encode a total of 80,000 to 100,000 proteins which differ in their sequence and function.

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References

- Expansion of the eukaryotic proteome by alternative splicing.

Biochemistry	Hematology & Oncology	Gene expression
Subject	System	Topic

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A 28-year-old man comes to the emergency department due to anxiety, weakness, dyspnea, and headaches. He is a graduate student in chemistry and was accidentally exposed to nitrites in his research laboratory. Physical examination is notable for cyanosis that is not improved by administration of supplemental oxygen via facemask. Analysis of a sample of arterial blood drawn from this patient prior to any oxygen supplementation is most likely to reveal normal values for which of the following?

A. Bound fraction of oxygen in the arterial blood

B. Oxygen carrying capacity of the arterial blood

C. Oxygen content of the arterial blood

D. Oxygen delivery to peripheral tissues

E. Partial pressure of oxygen in the arterial blood

Submit

A 28-year-old man comes to the emergency department due to anxiety, weakness, dyspnea, and headaches. He is a graduate student in chemistry and was accidentally exposed to nitrites in his research laboratory. Physical examination is notable for cyanosis that is not improved by administration of supplemental oxygen via facemask. Analysis of a sample of arterial blood drawn from this patient prior to any oxygen supplementation is most likely to reveal normal values for which of the following?

- A. Bound fraction of oxygen in the arterial blood (6%)
- B. Oxygen carrying capacity of the arterial blood (16%)
- C. Oxygen content of the arterial blood (15%)
- D. Oxygen delivery to peripheral tissues (2%)
- ✓ E. Partial pressure of oxygen in the arterial blood (59%)

Omitted
Correct answer
E

59%
Answered correctly

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02/05/2020
Last Updated

Explanation

Methemoglobin

Drugs
(Nitrites)

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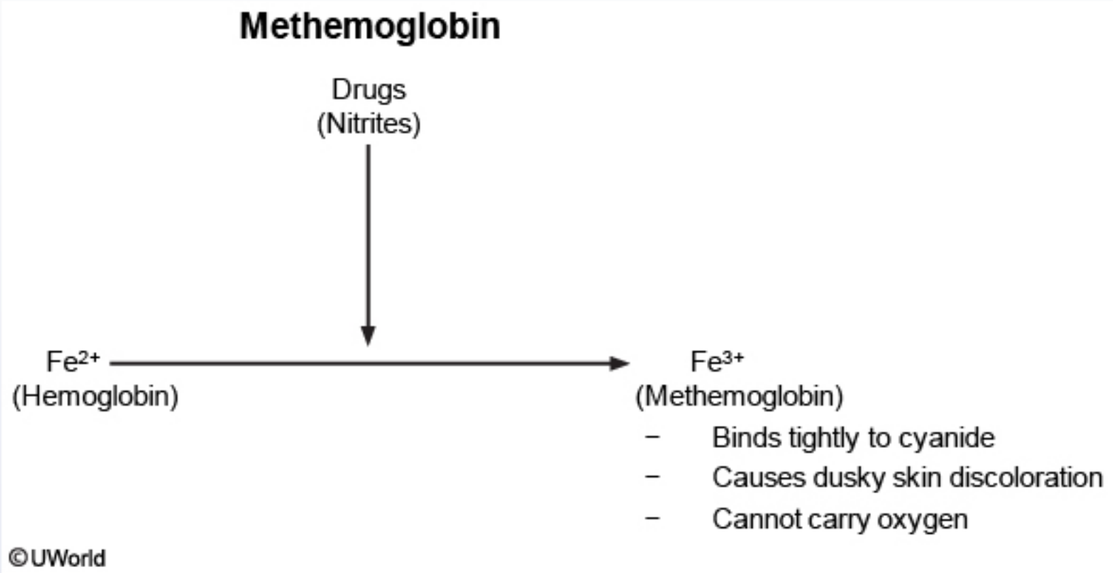

Iron bound to heme is normally in the **reduced** ferrous (Fe^{2+}) state. **Nitrites** cause poisoning by inducing the conversion of this heme iron to the **oxidized** ferric (Fe^{3+}) state, leading to the formation of **methemoglobin**. With iron in the oxidized ferric state, methemoglobin is unable to bind oxygen. In addition, the affinity of any residual ferrous iron in the hemoglobin tetramer is increased, causing a leftward shift of the oxygen-dissociation curve. However, the **partial pressure of oxygen** in blood, which represents the amount of oxygen dissolved in the plasma, is **unchanged**.

Methemoglobinemia causes **dusky** discoloration of the skin (similar to cyanosis), and because methemoglobin is unable to carry oxygen, a state of functional anemia is induced.

	PO_2 (dissolved oxygen)	**% Saturation of Hb**	**Total O_2 content** (both dissolved & O_2 attached to Hb)

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Methemoglobinemia causes **dusky** discoloration of the skin (similar to cyanosis), and because methemoglobin is unable to carry oxygen, a state of functional anemia is induced.

	PO_2 (dissolved oxygen)	**% Saturation of Hb**	**Total O_2 content** (both dissolved & O_2 attached to Hb)
CO poisoning	Normal	Decreased (CO competes with O_2)	Decreased
Anemia (low Hb)	Normal	Normal	Decreased
Polycythemia (high Hb)	Normal	Normal	Increased

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(Choices A, B, C, and D) Methemoglobin cannot bind to oxygen and therefore the oxygen content and oxygen carrying capacity of the arterial blood will decrease. The bound fraction of oxygen and oxygen delivery to the peripheral tissues will also decrease due to methemoglobin's inability to carry and deliver oxygen.

Educational objective:
Methemoglobinemia causes dusky discoloration of the skin (similar to cyanosis), and because methemoglobin is unable to carry oxygen, a state of functional anemia is induced. However, the blood partial pressure of oxygen will be unchanged as it is a measure of oxygen dissolved in plasma and is unrelated to hemoglobin function.

	(dissolved oxygen)	% Saturation of Hb	(both dissolved & O_2 attached to Hb)
CO poisoning	Normal	Decreased (CO competes with O_2)	Decreased
Anemia (low Hb)	Normal	Normal	Decreased
Polycythemia (high Hb)	Normal	Normal	Increased

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Biochemistry	Hematology & Oncology	Methemoglobinemia
Subject	System	Topic

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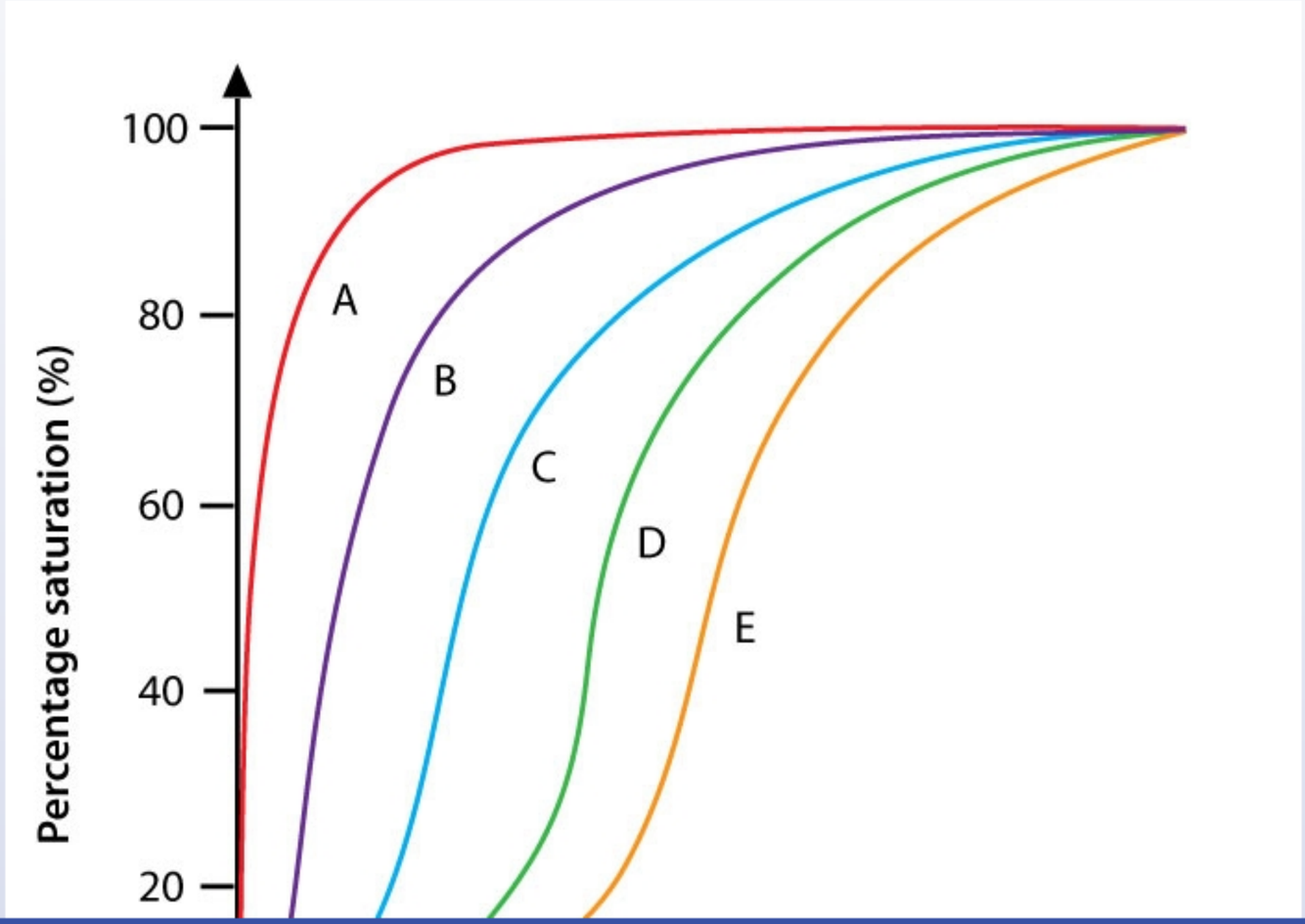
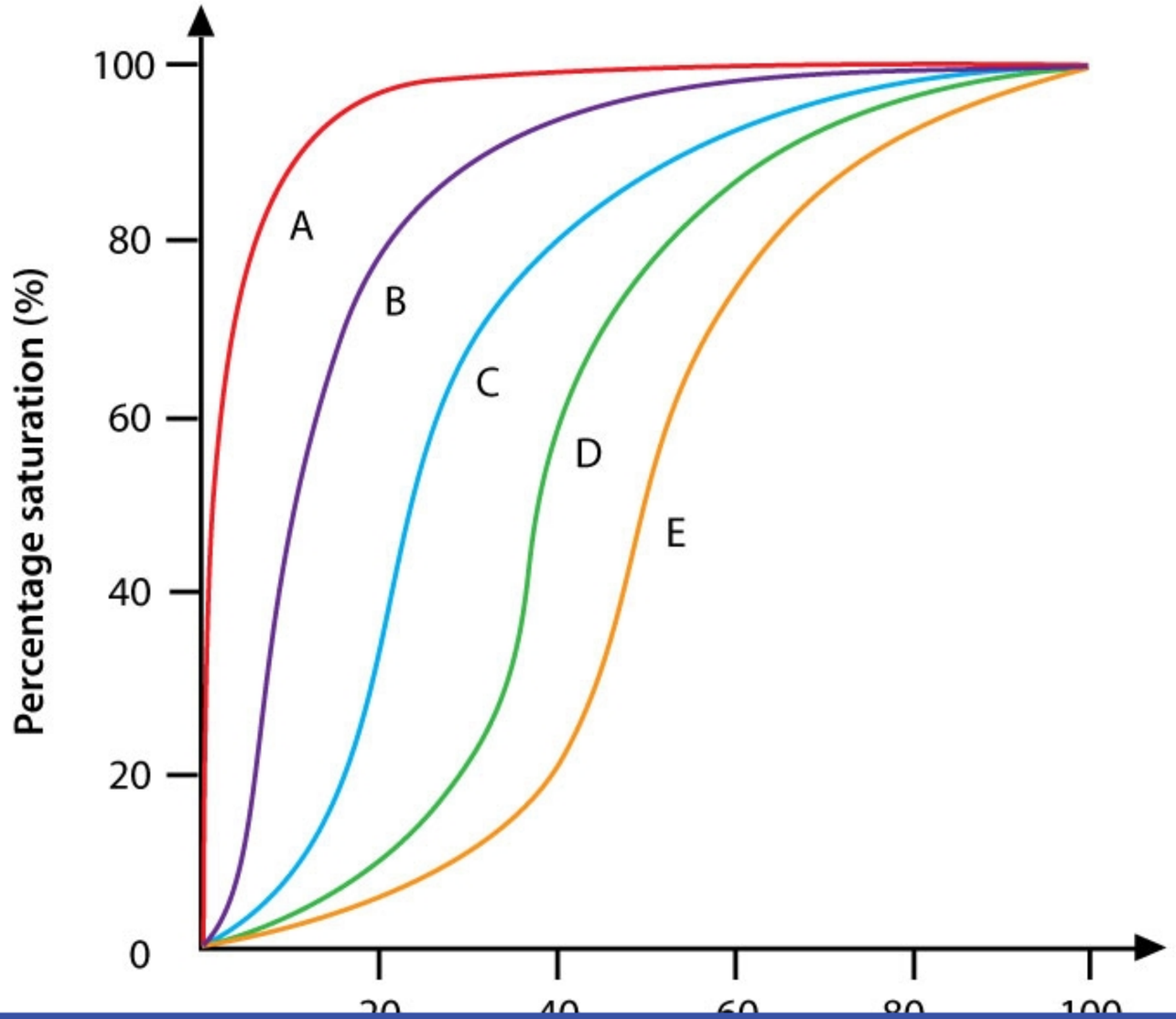
Scientists studying the principles behind oxygen-hemoglobin dissociation have discovered a way to successfully separate hemoglobin tetramers into individual alpha and beta subunits. During an experiment, a solution is created that contains only monomeric beta-hemoglobin subunits under physiologic conditions. If measured, the oxygen dissociation curve of the dissolved beta subunits will most likely resemble which of the following lines?

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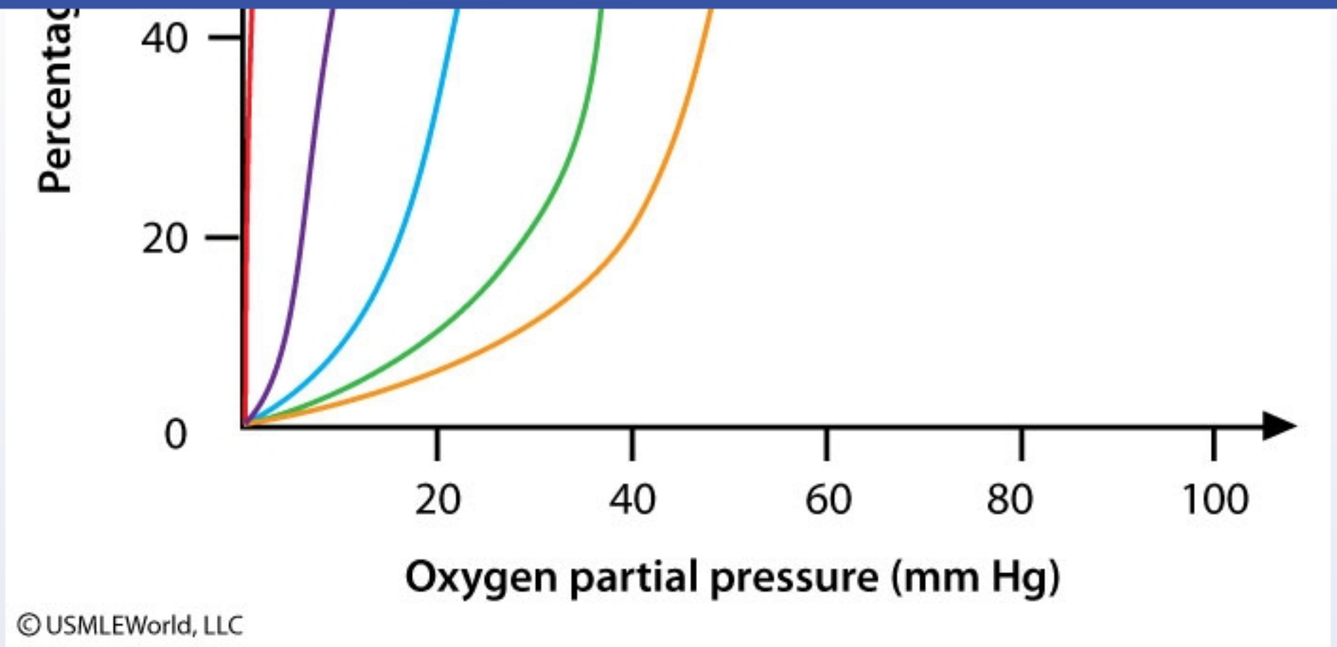

A. Line A
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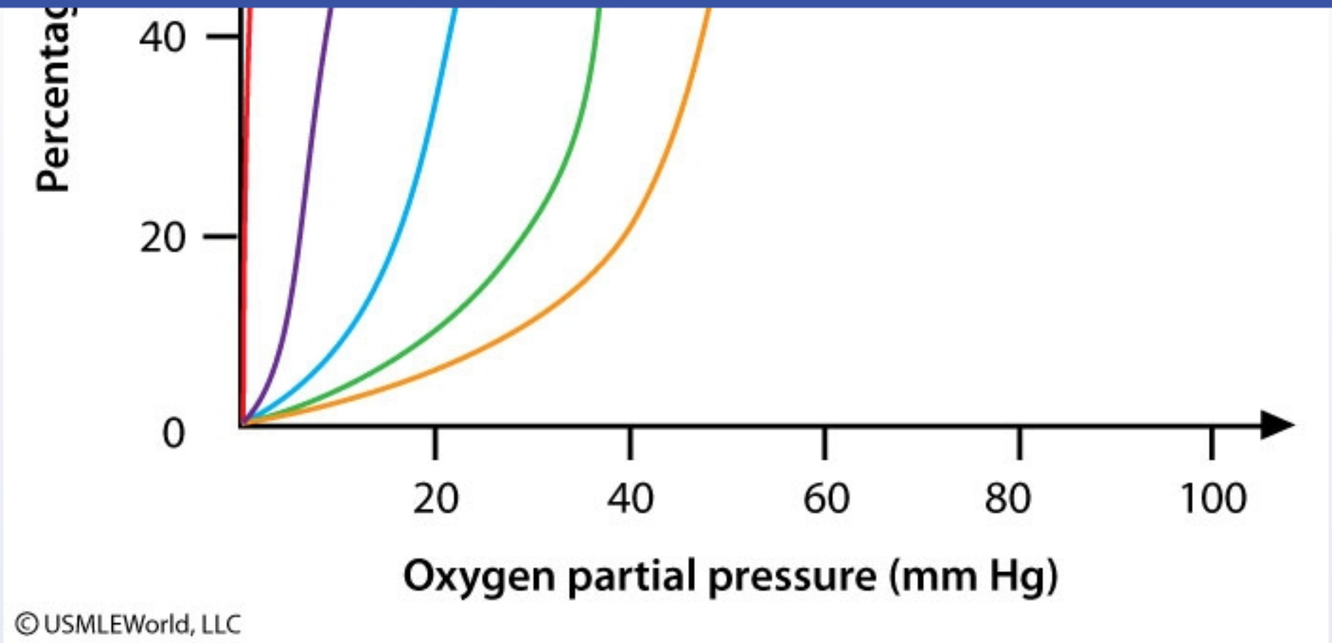

- ✓ A. Line A (52%)
- B. Line B (9%)
- C. Line C (8%)
- D. Line D (8%)
- E. Line E (20%)

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Correct answer

52%
Answered correctly

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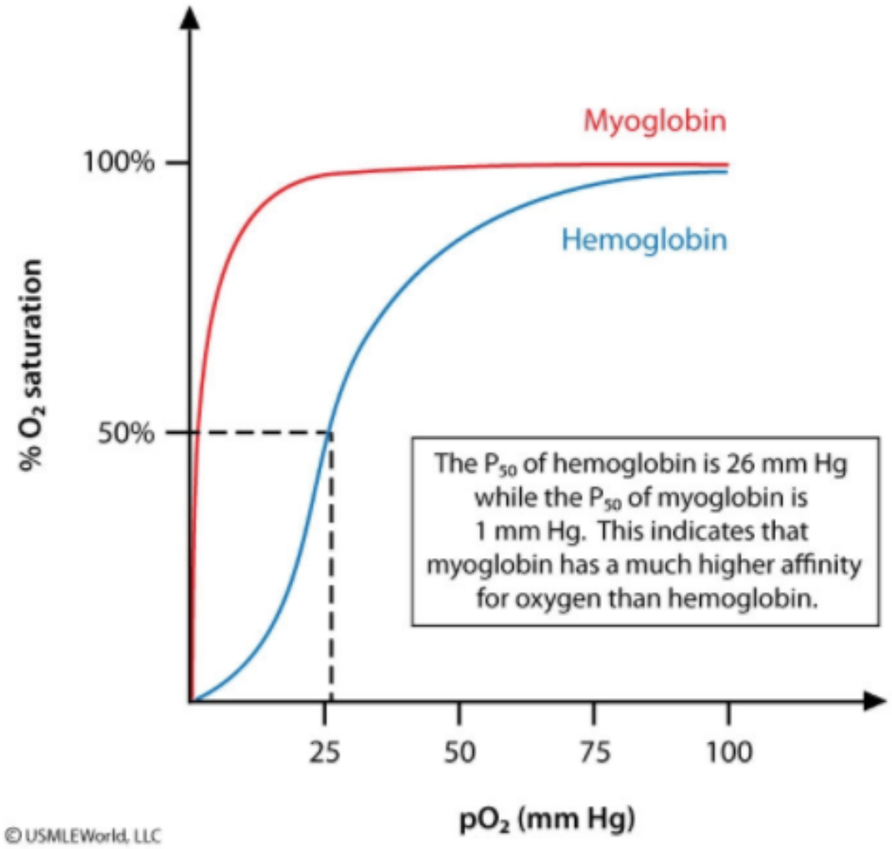
Oxygen-dissociation curves of hemoglobin & myoglobin



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Hemeproteins such as hemoglobin and myoglobin contain heme groups that are used to reversibly bind oxygen for transportation and storage. Hemoglobin A (the major form of hemoglobin in adults) is a tetramer consisting of 2 alpha and 2 beta chains. Each hemoglobin subunit is associated with a heme moiety, so each hemoglobin molecule has 4 heme groups. After binding to 1 oxygen molecule, the oxygen affinity of other heme molecules increases; this heme-heme interaction is responsible for the characteristic sigmoid shape of the oxygen-hemoglobin dissociation curve.

In contrast to hemoglobin, myoglobin is a monomeric protein and the primary oxygen-storing protein in skeletal and cardiac muscle tissue; it is only found in the bloodstream after muscle injury. The partial pressure of oxygen at which 50% of myoglobin molecules are oxygen saturated (P_{50}) is only 1 mm Hg, which is much lower than the P_{50} of hemoglobin (26 mm Hg). Myoglobin also has only a single heme group and so does not experience heme-heme interactions; therefore, its oxygen-dissociation curve is hyperbolic.

The secondary and tertiary structures of myoglobin and the hemoglobin beta subunit are almost identical (the α-subunits are also very similar to myoglobin). Because individual hemoglobin subunits are structurally similar to myoglobin, their oxygen-binding behavior is also similar. That is, if a hemoglobin molecule is dissociated, the individual subunits will have a hyperbolic oxygen-dissociation curve **(Choice A)**.

(Choice B) Line B is left-shifted compared to normal hemoglobin A, which could indicate a high oxygen affinity hemoglobin (eg, fetal hemoglobin). Hemoglobin A will also undergo a left shift in the presence of factors such as increased pH, decreased temperature, and decreased 2,3-diphosphoglycerate.

(Choice C) Line C depicts the normal oxygen-hemoglobin dissociation curve, with the typical sigmoidal relationship of pO_2 to hemoglobin O_2 saturation.

(Choices D and E) Lines D and E are shifted to the right, indicating a low oxygen affinity hemoglobin. Hemoglobin A has low affinity for oxygen under conditions such as decreased pH, increased temperature, and increased 2,3-diphosphoglycerate.

Educational objective:
The individual subunits of the hemoglobin molecule are structurally analogous to myoglobin. If separated, the monomeric subunits will demonstrate a hyperbolic oxygen-dissociation curve similar to that of myoglobin.

References

is only 1 mm Hg, which is much lower than the P_{50} of hemoglobin (26 mm Hg). Myoglobin also has only a single heme group and so does not experience heme-heme interactions; therefore, its oxygen-dissociation curve is hyperbolic.

The secondary and tertiary structures of myoglobin and the hemoglobin beta subunit are almost identical (the α-subunits are also very similar to myoglobin). Because individual hemoglobin subunits are structurally similar to myoglobin, their oxygen-binding behavior is also similar. That is, if a hemoglobin molecule is dissociated, the individual subunits will have a hyperbolic oxygen-dissociation curve **(Choice A)**.

(Choice B) Line B is left-shifted compared to normal hemoglobin A, which could indicate a high oxygen affinity hemoglobin (eg, fetal hemoglobin). Hemoglobin A will also undergo a left shift in the presence of factors such as increased pH, decreased temperature, and decreased 2,3-diphosphoglycerate.

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(Choices D and E) Lines D and E are shifted to the right, indicating a low oxygen affinity hemoglobin. Hemoglobin A has low affinity for oxygen under conditions such as decreased pH, increased temperature, and increased 2,3-diphosphoglycerate.

Educational objective:
The individual subunits of the hemoglobin molecule are structurally analogous to myoglobin. If separated, the monomeric subunits will demonstrate a hyperbolic oxygen-dissociation curve similar to that of myoglobin.

References

- Myoglobin oxygen dissociation by multiwavelength spectroscopy.
- Configuration of the hemoglobin oxygen dissociation curve demystified: a basic mathematical proof for medical and biological sciences undergraduates.

Biochemistry	Hematology & Oncology	Hemoglobin properties
Subject	System	Topic

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A 24-year-old man is evaluated for episodic anemia, jaundice, and dark urine. These episodes typically occur after the use of certain drugs or following infection. Additional history reveals that he has a brother who experiences similar episodes. Peripheral blood smear reveals red blood cells with the findings shown below.

Deficiency of which of the following enzymes would most likely result in a condition similar to this patient's presentation?

A. Bisphosphoglycerate mutase
B. Glutathione reductase
C. Hexokinase
D. Pyruvate kinase
E. Transketolase

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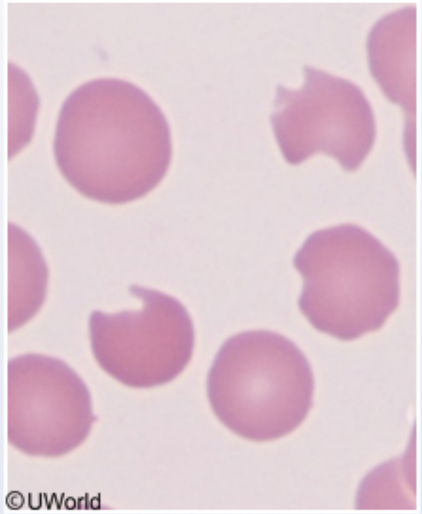

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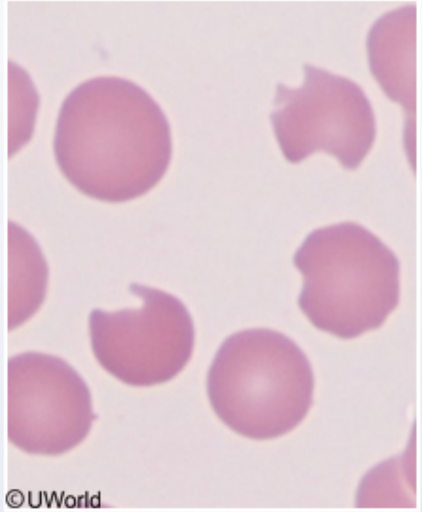

Deficiency of which of the following enzymes would most likely result in a condition similar to this patient's presentation?

- A. Bisphosphoglycerate mutase (2%)
- ✓ B. Glutathione reductase (74%)
- C. Hexokinase (2%)
- D. Pyruvate kinase (14%)
- E. Transketolase (5%)

Omitted
Correct answer

74%
Answered correctly

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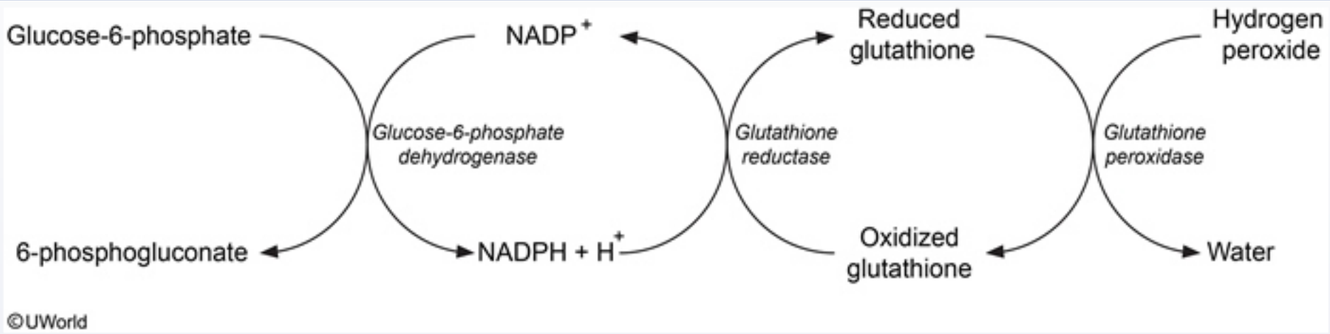

This patient likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**, an X-linked recessive disorder causing hemolytic anemia and jaundice in response to oxidant stressors (eg, sulfonamide & antimalarial drugs, infection). Heinz bodies (oxidized hemoglobin conglomerates) precipitate in red blood cells and are removed by splenic macrophages, leaving behind characteristic bite cells.

G6PD is an enzyme of the **pentose phosphate pathway**. It generates the reducing agent **NADPH**, which is essential for detoxification of hydrogen peroxide produced by partial reduction of molecular oxygen in red blood cells. In the absence of NADPH, **reduced glutathione** (the molecule required for reduction of hydrogen peroxide to water) remains in an oxidized state, and red blood cells become susceptible to oxidative damage.

Glutathione reductase catalyzes the reduction of oxidized glutathione. Its absence leads to an inability to use NADPH to reduce glutathione, resulting in a clinical scenario **similar** to G6PD deficiency.

(Choice A) Bisphosphoglycerate mutase is an enzyme unique to red blood cells and placental cells. It catalyzes the production of 2,3-bisphosphoglycerate, a molecule that binds to hemoglobin and increases offloading of oxygen in the tissues.

(Choices C and D) Deficiency of the glycolytic enzymes hexokinase and pyruvate kinase leads to hemolytic anemia due to lack of ATP generation. However, these conditions would not present with bite cells and the hemolysis is not associated with exposure to oxidant stressors.

(Choice E) Transketolase, along with transaldolase, catalyzes the nonoxidative reactions of the pentose phosphate pathway, producing the ribose sugar necessary for nucleotide synthesis. The reducing equivalent NADPH is not generated in this portion of the pathway.

Educational objective:

This patient likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**, an X-linked recessive disorder causing hemolytic anemia and jaundice in response to oxidant stressors (eg, sulfonamide & antimalarial drugs, infection). Heinz bodies (oxidized hemoglobin conglomerates) precipitate in red blood cells and are removed by splenic macrophages, leaving behind characteristic bite cells.

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(Choice E) Transketolase, along with transaldolase, catalyzes the nonoxidative reactions of the pentose phosphate pathway, producing the ribose sugar necessary for nucleotide synthesis. The reducing equivalent NADPH is not generated in this portion of the pathway.

Educational objective:
Glucose 6-phosphate dehydrogenase deficiency causes hemolytic anemia and jaundice secondary to increased oxidative stress due to the lack of NADPH. Glutathione reductase deficiency has a similar clinical consequence as its absence results in an inability to utilize NADPH to reduce glutathione.

Biochemistry	Hematology & Oncology	G6PD deficiency
Subject	System	Topic

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An infant born to a Greek immigrant appears healthy at birth but develops transfusion-dependent hemolytic anemia by the age of 6 months. His erythrocytes contain insoluble aggregates of hemoglobin subunits. The child developed normally in utero because at that time he produced high quantities of:

A. α-globin
B. β-globin
C. γ-globin
D. δ-globin
E. ζ-globin

Submit

An infant born to a Greek immigrant appears healthy at birth but develops transfusion-dependent hemolytic anemia by the age of 6 months. His erythrocytes contain insoluble aggregates of hemoglobin subunits. The child developed normally in utero because at that time he produced high quantities of:

- A. α-globin (3%)
- B. β-globin (3%)
- ✓ C. γ-globin (84%)
- D. δ-globin (5%)
- E. ζ-globin (3%)

Omitted
Correct answer
C

84%
Answered correctly

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Explanation

In adults, hemoglobin A is the predominant form of hemoglobin. It is a tetramer consisting of two alpha and two beta chains. Normally the synthesis of alpha and beta chains is tightly regulated such that one α-chain is synthesized for every β-chain. Hemoglobin formation begins within a few weeks of conception. The initial hemoglobin formed by a fetus in utero is called embryonic hemoglobin (Gower). This hemoglobin is composed of two zeta (ζ) and two epsilon (ε) chains (ζ2ε2) and is produced in the embryonic yolk sac. Within a few weeks the fetal liver starts synthesizing hemoglobin F (fetal hemoglobin). This form of hemoglobin is composed of two alpha and two gamma chains (α2γ2). HbF is the major hemoglobin in the fetus during last few months of gestation and in infants during first few weeks of postnatal life. HbA synthesis starts

In adults, hemoglobin A is the predominant form of hemoglobin. It is a tetramer consisting of two alpha and two beta chains. Normally the synthesis of alpha and beta chains is tightly regulated such that one α-chain is synthesized for every β-chain. Hemoglobin formation begins within a few weeks of conception. The initial hemoglobin formed by a fetus in utero is called embryonic hemoglobin (Gower). This hemoglobin is composed of two zeta (ζ) and two epsilon (ε) chains (ζ2ε2) and is produced in the embryonic yolk sac. Within a few weeks the fetal liver starts synthesizing hemoglobin F (fetal hemoglobin). This form of hemoglobin is composed of two alpha and two gamma chains (α2γ2). HbF is the major hemoglobin in the fetus during last few months of gestation and in infants during first few weeks of postnatal life. HbA synthesis starts during the final month of gestation and gradually replaces HbF during postnatal life. Knowing the chronology of fetal hemoglobin formation and the gradual transition to adult hemoglobin (HbA) is important in understanding the relationship between clinical manifestations and postnatal age in beta thalassemia.

Thalassemias are hereditary hemolytic anemias resulting from defective synthesis of globin chains. As described above, the synthesis of alpha and beta globin chains is very coordinated. In patients with thalassemia, the synthesis of either alpha or beta chains is defective. Beta thalassemia is caused by defective synthesis of beta chains. There are two copies of the beta globin gene (one from each parent). If only one gene is defective the patient will have beta thalassemia trait (beta thalassemia minor) and lack significant anemia. A defect in both beta globin genes results in severe hemolytic anemia known as beta thalassemia major. In this disease, alpha chains are produced normally but they cannot form stable tetramers due to the lack of beta globin chains. This failure to form stable hemoglobin leads to precipitation of alpha globin chains and premature lysis of red blood cells. Beta thalassemia cannot become symptomatic as long as there are significant amounts of gamma chains present because gamma chains make up for the absence of HbA beta chains in forming tetramers. Thus, in late gestation and early postnatal life, the expression of hemoglobin A is offset by gamma chain production **(Choice C)**. As gamma chain production wanes, patients will become symptomatic.

(Choice A) α-globin is a normal component of both HbA and HbF. α-globin synthesis is defective in α-thalassemia but it is normal in β-thalassemia. α-globin is able to combine with γ-globin to form HbF. This allows patients with β-thalassemia major to be asymptomatic in utero and in the first few months following birth.

(Choice B) β-globin synthesis is defective in patients with b-thalassemia.

(Choice D) δ-globin is a minor globin gene that is expressed at very low levels in normal adults. Two α-globins and two δ-globins combine to form hemoglobin A2.

and beta globin chains is very coordinated. In patients with thalassemia, the synthesis of either alpha or beta chains is defective. Beta thalassemia is caused by defective synthesis of beta chains. There are two copies of the beta globin gene (one from each parent). If only one gene is defective the patient will have beta thalassemia trait (beta thalassemia minor) and lack significant anemia. A defect in both beta globin genes results in severe hemolytic anemia known as beta thalassemia major. In this disease, alpha chains are produced normally but they cannot form stable tetramers due to the lack of beta globin chains. This failure to form stable hemoglobin leads to precipitation of alpha globin chains and premature lysis of red blood cells. Beta thalassemia cannot become symptomatic as long as there are significant amounts of gamma chains present because gamma chains make up for the absence of HbA beta chains in forming tetramers. Thus, in late gestation and early postnatal life, the expression of hemoglobin A is offset by gamma chain production **(Choice C)**. As gamma chain production wanes, patients will become symptomatic.

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(Choice B) β-globin synthesis is defective in patients with b-thalassemia.

(Choice D) δ-globin is a minor globin gene that is expressed at very low levels in normal adults. Two α-globins and two δ-globins combine to form hemoglobin A2.

(Choice E) ζ-globin is a component of hemoglobin Gower, the initial hemoglobin formed by the embryo very early in embryogenesis.

Educational Objective:
HbF contains γ-globin instead of β-globin. Patients with homozygotic β-thalassemia (β-thalassemia major) are asymptomatic at birth due to the presence of γ-globins and HbF. Switching to HbA production and the cessation of γ-globin synthesis precipitates the symptoms of β-thalassemia.

Biochemistry	Hematology & Oncology	Thalassemia
Subject	System	Topic

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A 34-year-old man comes to the emergency department due to a facial injury. He reports getting hit on the face during a fistfight at a bar. Examination shows dark blue periorbital ecchymosis on the right side. Ophthalmic and neurologic examinations are otherwise normal. After appropriate evaluation, the patient is discharged home. Several days later, the bruise becomes greenish in color. This change in color is best explained by the activity of which of the following enzymes?

A. Bilirubin glucuronyl transferase
B. Ferrochelatase
C. Heme oxygenase
D. Porphobilinogen deaminase
E. Uroporphyrinogen decarboxylase

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A. Bilirubin glucuronyl transferase (17%)
B. Ferrochelatase (8%)
✓ C. Heme oxygenase (54%)
D. Porphobilinogen deaminase (12%)
E. Uroporphyrinogen decarboxylase (6%)

Omitted
Correct answer
C

54%
Answered correctly

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Explanation

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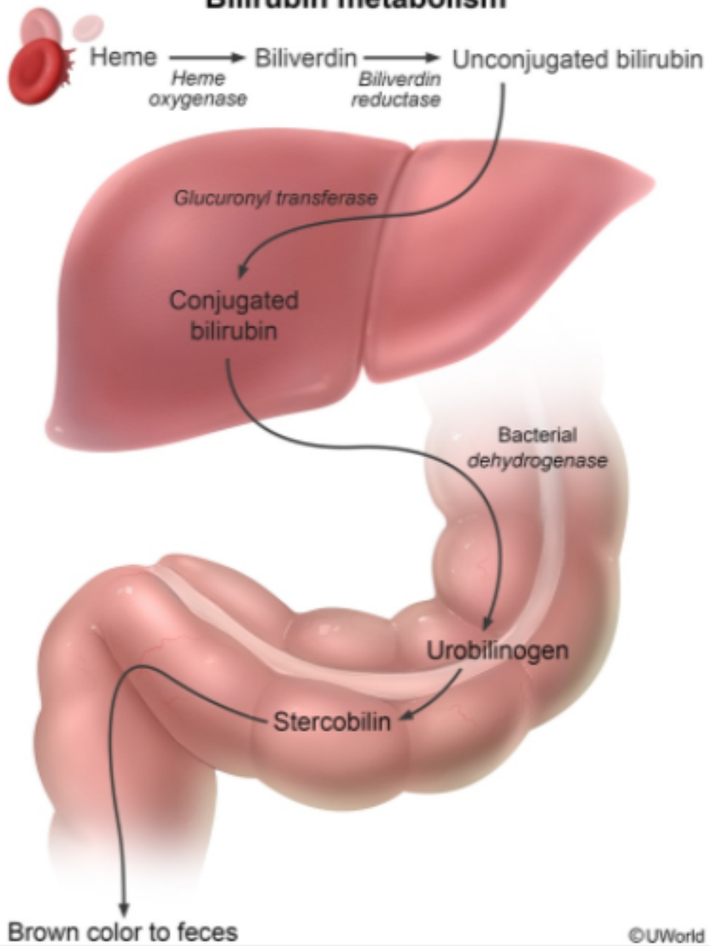

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This patient has a resolving **hematoma** after a traumatic injury. Following the injury, hemoglobin-containing erythrocytes escape into the periorbital tissues, giving the bruise its initial purple or bluish color. Erythrocyte destruction causes the release of iron-containing heme molecules. **Heme oxygenase** (contained in macrophages, among other cells) degrades heme into **biliverdin**, carbon monoxide, and ferrous iron while consuming oxygen and electrons provided by NADH and NADPH-cytochrome P450 reductase. Biliverdin is **green** in color and is further reduced (by the enzyme biliverdin reductase) to the yellow pigment bilirubin, which is then transported to the liver bound to albumin.

(Choice A) Bilirubin glucuronyl transferase, or uridine 5'-diphospho-glucuronyl transferase (UGT), is the enzyme necessary for bilirubin conjugation to glucuronic acid. Lack of UGT or the use of medications that interfere with its activity impairs the liver's ability to conjugate bilirubin.

(Choices B, D, and E) Ferrochelatase (inhibited by lead) is the final enzyme in the heme synthetic pathway. Porphobilinogen deaminase (PBG deaminase) and uroporphyrinogen decarboxylase (UROD) are also involved in heme production, not degradation; UROD deficiency can be seen in porphyria cutanea tarda, the most common porphyria, and PBG deaminase deficiency can be seen in acute intermittent porphyria.

Educational objective:
Heme oxygenase converts heme to biliverdin, a pigment that causes the greenish color to develop in bruises several days after an injury.

Biochemistry	Hematology & Oncology	Heme metabolism
Subject	System	Topic

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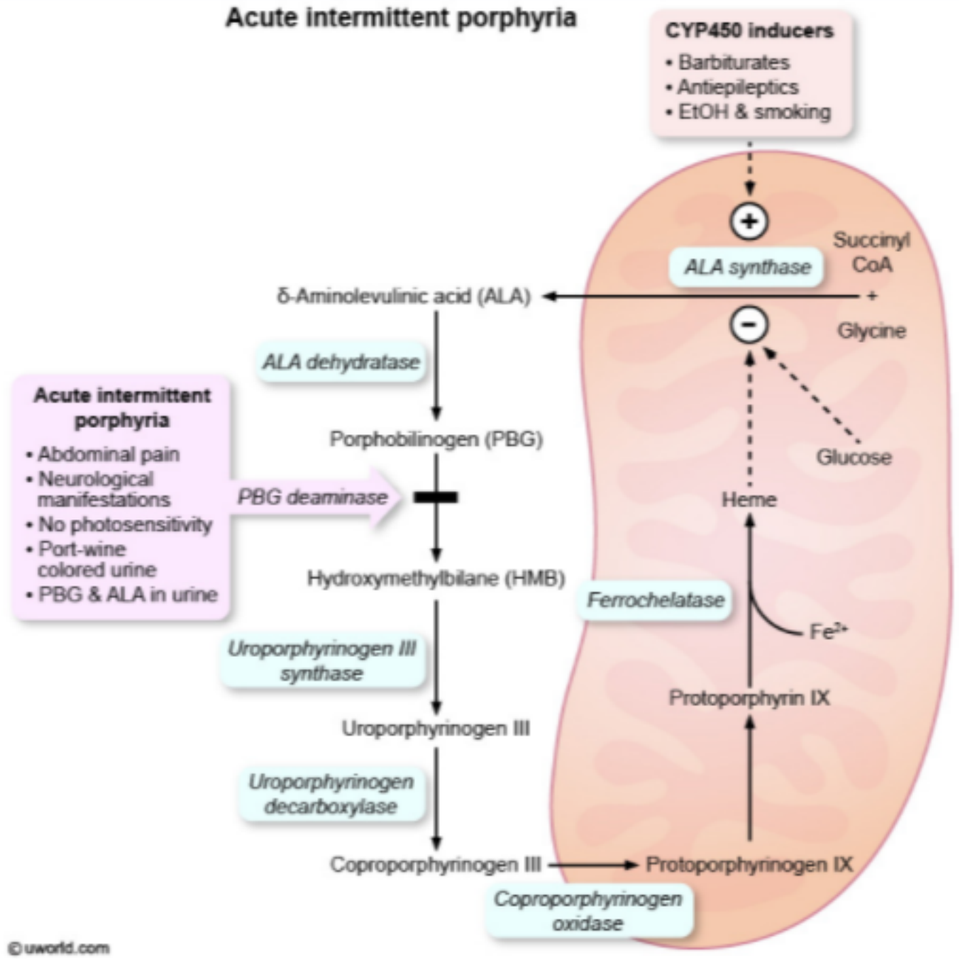

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A 34-year-old woman comes to the office after her sister was diagnosed with breast cancer. She has no nipple discharge, breast lumps, or discomfort. Breast examination is normal. Her sister was found to have a multiple base pair insertion affecting exon 11 of the *BRCA1* gene that leads to a frameshift mutation. A screening test to evaluate for a similar insertion mutation in the patient's *BRCA1* gene is performed. The test uses polymerase chain reaction (PCR) to amplify the target exon and gel electrophoresis to assess the size of the exon compared to the wild-type allele. Which of the following must be known in order to perform the amplification part of this analysis?

- A. Restriction enzyme susceptibility sites within the target exon
- B. The amino acid sequence of the abnormal BRCA1 protein
- C. The cDNA nucleotide sequence
- D. The complete nucleotide sequence of the target exon
- E. The nucleotide sequence of the regions flanking the target exon

Submit

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- A. Restriction enzyme susceptibility sites within the target exon (14%)
- B. The amino acid sequence of the abnormal BRCA1 protein (10%)
- C. The cDNA nucleotide sequence (13%)
- D. The complete nucleotide sequence of the target exon (12%)
- ✓ E. The nucleotide sequence of the regions flanking the target exon (49%)

Omitted
Correct answer
E

49%
Answered correctly

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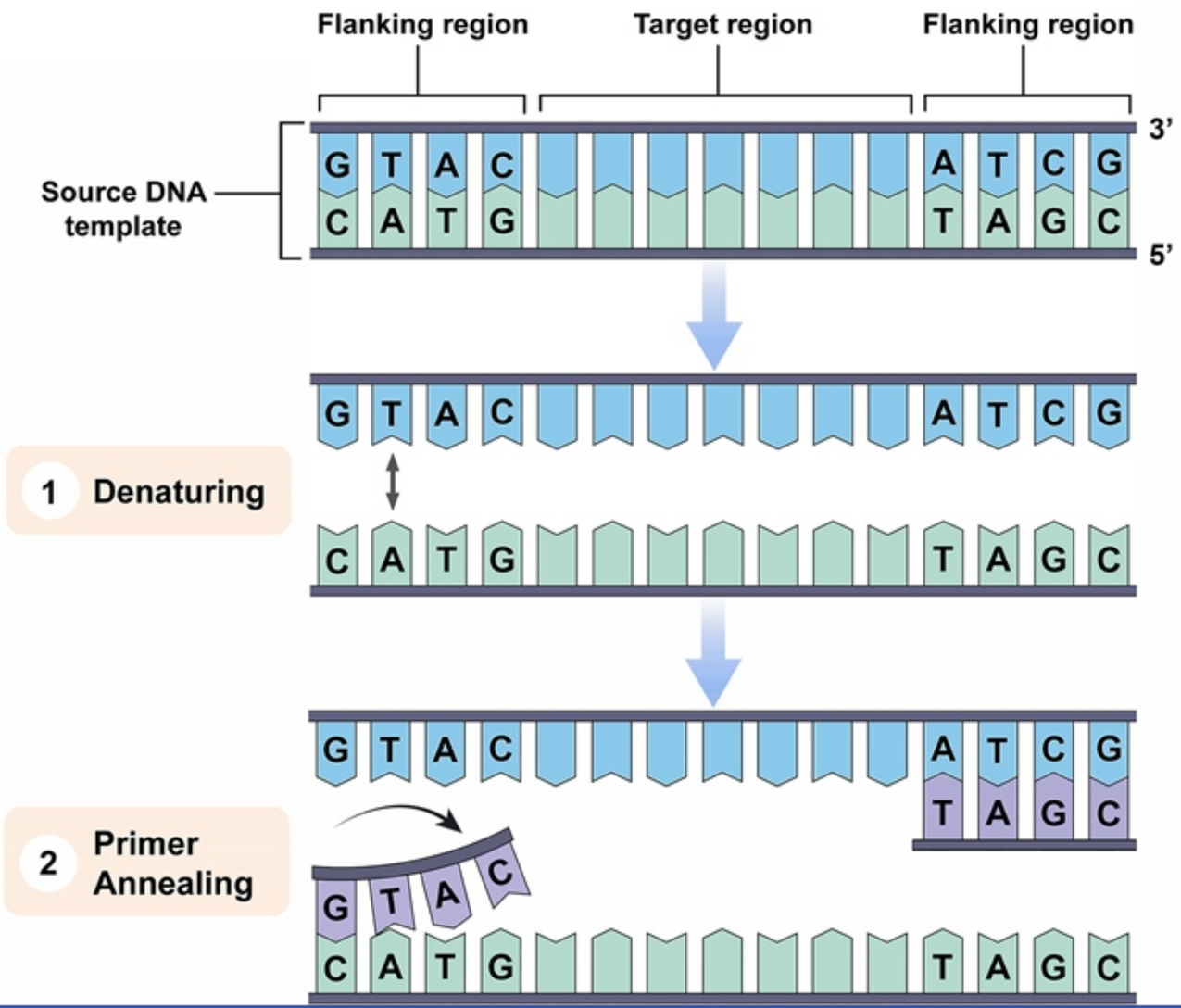
Explanation

Polymerase chain reaction



Polymerase chain reaction

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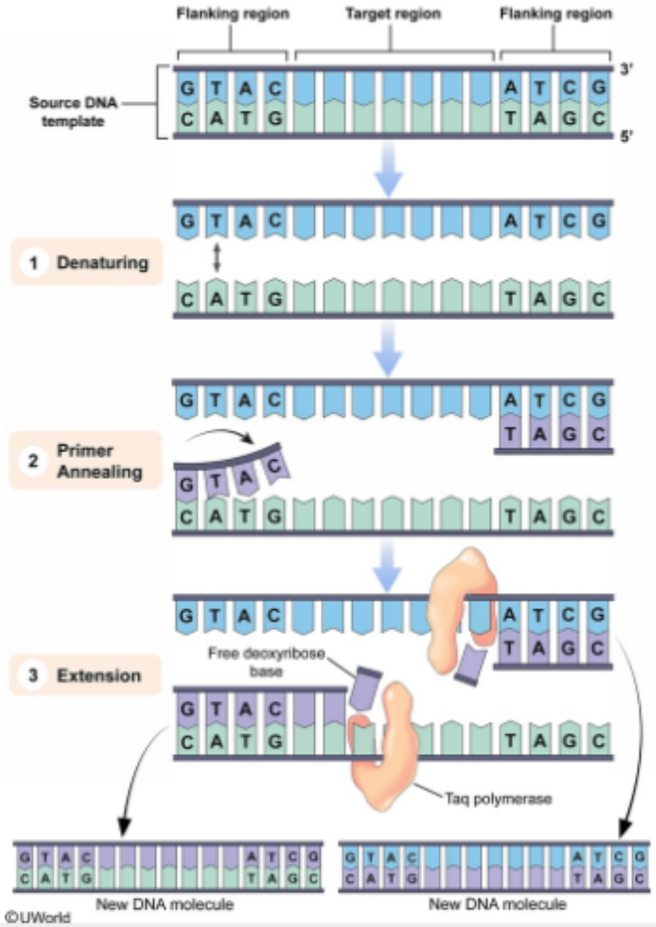
Polymerase chain reaction



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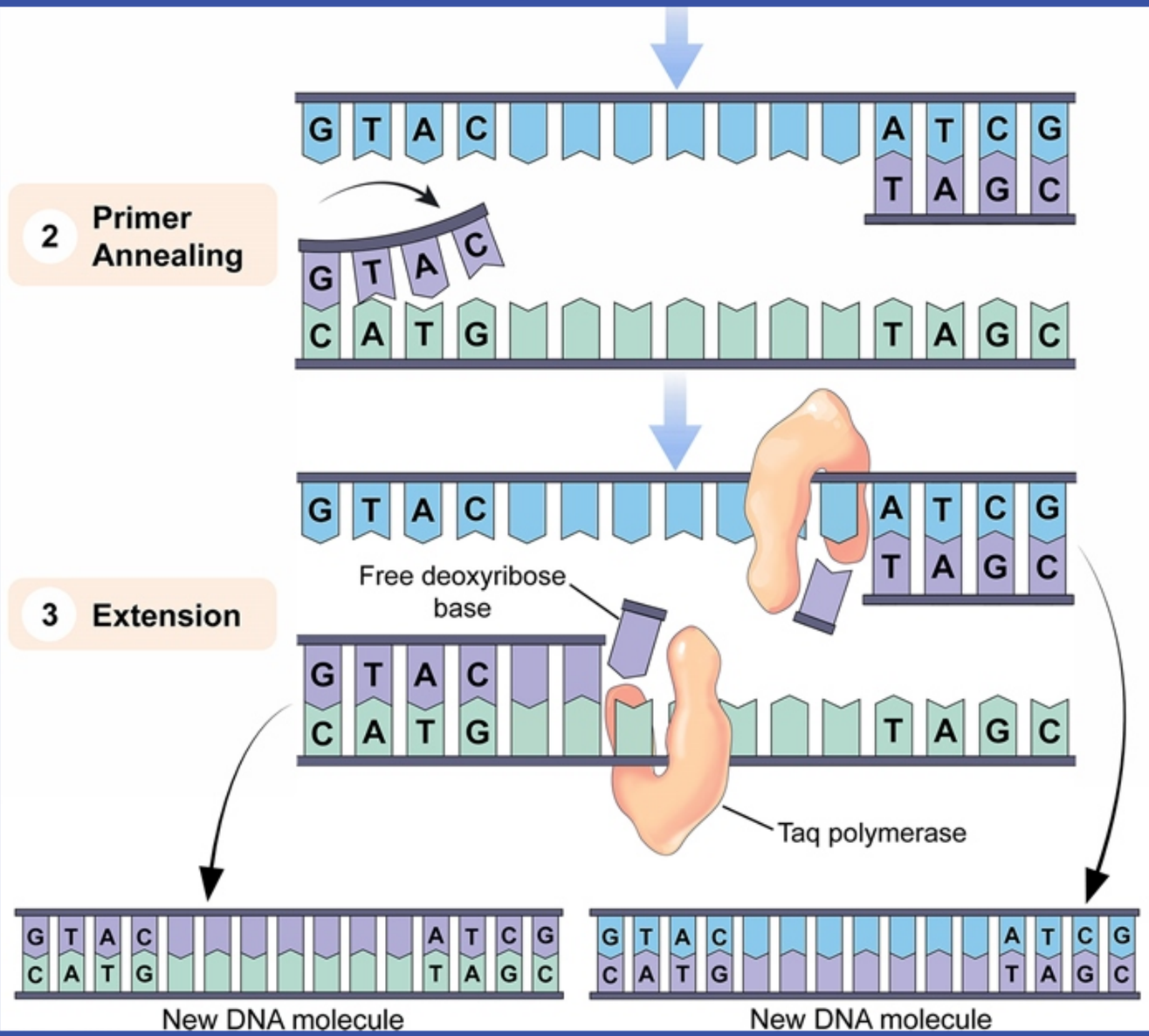
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Taq polymerase
New DNA molecule
New DNA molecule

Polymerase chain reaction (PCR) is used to **amplify** small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. Several elements are required for PCR. The first is a source **DNA template** that includes the target region to be amplified (eg, *BRCA1* exon 11) as well as flanking sequences adjacent to the target region. The oligonucleotide sequence of these flanking regions must be known in order to make the **primers** necessary to start PCR. However, the exact nucleotide sequence of the target region does **not** need to be known **(Choice D)**. A thermostable **DNA polymerase** (not denatured at high temperatures) is then used to replicate the DNA template from a pool of supplied **deoxynucleotide triphosphates** using the following 3 steps:

1. **Denaturing**: Thermal separation of the DNA template is accomplished by exposing the sample to high temperatures
2. **Annealing**: Primers combine with the denatured, single-stranded flanking ends of the target region when the temperature is lowered
3. **Elongation**: DNA polymerase forms new daughter DNA strands in the 5' to 3' direction, starting from the 3' end of each primer

These steps are repeated to obtain millions of copies of the target DNA segment in a short period of time (exponential amplification).

(Choice A) Restriction sites are cleaved by specific endonucleases and can be used to identify polymorphisms within variant alleles on gel electrophoresis (restriction fragment length polymorphism analysis). However, knowing the restriction enzyme susceptibility sites within the target region is not necessary for PCR amplification.

(Choice B) In PCR, only DNA segments are amplified and studied; proteins are not involved. Proteins can be analyzed using Western blots, but even then, exact amino acid sequences do not need to be known.

(Choice C) Complementary DNA (cDNA) is produced by the reverse transcriptase enzyme using mRNA as a template in reverse transcriptase PCR; it is not used in regular PCR. cDNA can be used to express eukaryotic proteins in prokaryotes by transferring the cDNA into the genome of a recipient organism.

Educational objective:
Polymerase chain reaction is used to amplify small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. It requires primers that are complementary to the regions of DNA flanking the segment of interest. Thermostable DNA polymerase, deoxynucleotide triphosphates, and a source DNA template strand are also necessary.

Biochemistry Hematology & Oncology Polymerase chain reaction

A 17-year-old girl comes to the office for follow-up on anemia. She has taken iron supplements regularly since being diagnosed with iron deficiency anemia 3 months ago. However, the patient still feels fatigued and does not think that the supplements have improved her symptoms. She has occasional gingival bleeding when brushing her teeth. Menses occur every 27-28 days and last 7-8 days with heavy flow, sometimes requiring her to change pads every hour. Platelet count is normal. Further evaluation reveals that the patient's platelets do not agglutinate appropriately in response to ristocetin. When normal plasma is added to the solution of patient platelets and ristocetin, appropriate platelet agglutination occurs. Which of the following is most likely deficient in this patient?

- A. Glycoprotein Ib receptors
- B. Glycoprotein IIb-IIIa receptors
- C. Hageman factor
- D. Thromboxane A2
- E. Von Willebrand factor

Submit

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A. Glycoprotein Ib receptors (6%)

B. Glycoprotein IIb-IIIa receptors (13%)

C. Hageman factor (3%)

D. Thromboxane A2 (2%)

✓ E. Von Willebrand factor (73%)

Omitted
Correct answer
E

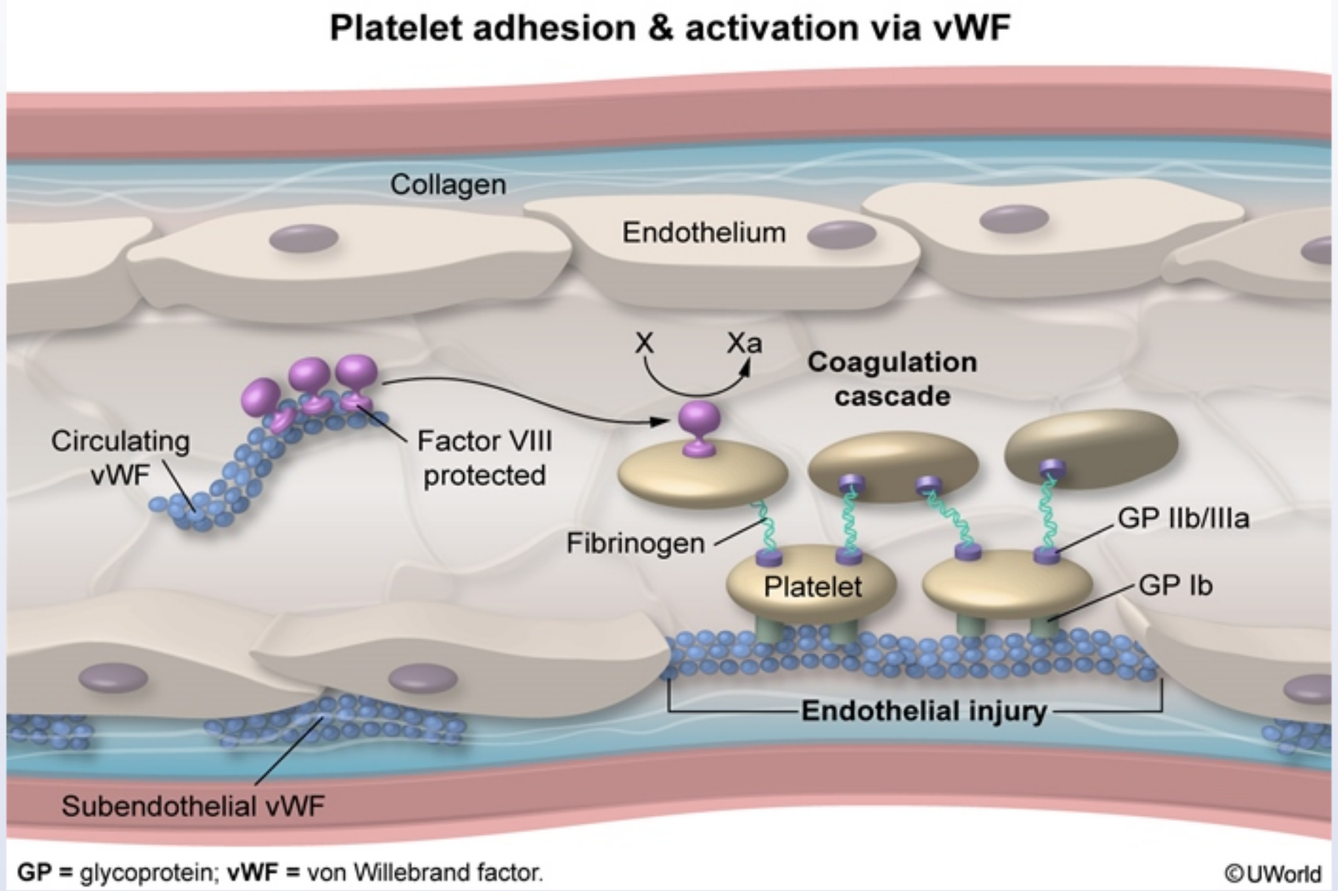
73%
Answered correctly

02 secs
Time Spent

05/12/2020
Last Updated

Explanation

Platelet adhesion & activation via vWF



Von Willebrand factor (vWF) is an important hemostatic glycoprotein (GP) synthesized by endothelial cells and megakaryocytes. Following endothelial damage, vWF **binds GP Ib receptors** on the platelet membrane and mediates **platelet adhesion** to subendothelial collagen. Deficiency of vWF impairs platelet adhesion and can lead to easy bruising and **prolonged mucocutaneous bleeding** (eg, gingival bleeding, heavy menses).

Laboratory workup in vWF deficiency reveals a normal platelet count and an **abnormal ristocetin cofactor assay**. The ristocetin cofactor assay

Laboratory workup in vWF deficiency reveals a normal platelet count and an **abnormal ristocetin cofactor assay**. The ristocetin cofactor assay measures in-vitro, vWF-dependent platelet agglutination (indicative of impaired platelet adhesion in-vivo). Ristocetin activates GP Ib receptors on platelets and makes them available for vWF binding; when the vWF level is decreased, there is **poor platelet agglutination in the presence of ristocetin**. When normal plasma that contains vWF is added, appropriate platelet agglutination occurs.

VWF also serves as a **carrier for factor VIII** to prolong its half-life, and vWF deficiency can lead to functional deficiency of factor VIII that further contributes to bleeding complications. PTT may be normal or prolonged depending on the degree of factor VIII impairment.

Combined oral contraceptives are often used for treatment of menorrhagia due to vWF deficiency. Patients can also be treated with desmopressin, which stimulates vWF release from endothelium.

(Choice A) Bernard-Soulier syndrome (hereditary deficiency of GP Ib receptors) is characterized by thrombocytopenia, enlarged platelets, and mucocutaneous bleeding. Platelet agglutination to ristocetin will be abnormal and, because the deficiency is with GP Ib receptors and not vWF, the addition of normal plasma will not correct the agglutination.

(Choice B) Hereditary deficiency of GP IIb/IIIa receptors occurs in Glanzmann thrombasthenia, which manifests with mucocutaneous bleeding. Platelet agglutination in response to ristocetin is normal because the levels of vWF and GP Ib receptors are normal.

(Choice C) Congenital deficiency of factor XII (Hageman) causes marked PTT prolongation; however, it does not cause clinical bleeding complications. Instead, patients may have a tendency for thromboembolic complications for unclear reasons.

(Choice D) Thromboxane A2 deficiency is associated with aspirin treatment due to irreversible inactivation of cyclooxygenase in platelets. The major effect is on GP IIb/IIIa-mediated platelet aggregation rather than GP Ib-mediated platelet adhesion; therefore, platelet agglutination to ristocetin is normal.

Educational objective:
Following endothelial damage, von Willebrand factor (vWF) binds glycoprotein Ib receptors on platelets to mediate platelet adherence. The ristocetin cofactor assay measures platelet agglutination via binding of glycoprotein Ib receptors to vWF; it will be abnormal in vWF deficiency but will correct with the addition of normal (vWF-containing) plasma.

References

desmopressin, which stimulates vWF release from endothelium.

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References

- Diagnosis and management of von Willebrand disease: guidelines for primary care.
- Of von Willebrand factor and platelets.

Biochemistry	Hematology & Oncology	Von willebrand disease
Subject	System	Topic

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A 2-day-old boy is being examined in the newborn nursery prior to discharge from the hospital. He was born at 38 weeks gestation by vaginal delivery. The pregnancy and delivery were uncomplicated, and the boy has been breastfeeding, stooling, and urinating normally. The patient's mother has beta-thalassemia trait, and his father has a normal hemoglobin electrophoresis. Vital signs and physical examination are normal. Which of the following hemoglobin compositions is most likely predominant in this infant?

- A. α2β2
- B. α2γ2
- C. α2δ2
- D. β4
- E. γ4
- F. ζ2ε2
- G. ζ2γ2

Submit

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- A. α2β2 (15%)
- ✓ B. α2γ2 (78%)
- C. α2δ2 (4%)
- D. β4 (0%)
- E. γ4 (0%)
- F. ζ2ε2 (0%)
- G. ζ2γ2 (0%)

Omitted
Correct answer
B

78%
Answered correctly

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Time Spent

06/14/2020
Last Updated

Explanation

Hemoglobin

Hemoglobin		
Type	**Name**	**Components**
Embryonic	Gower 1	ζ2ε2
	Portland	ζ2γ2
	Gower 2	α2ε2
Fetal	F*	α2γ2
Adult	A	α2β2
	A2*	α2δ2
α-thalassemia intermedia	H	β4
α-thalassemia major	Barts	γ4

*Predominant in β-thalassemia.

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Hemoglobin is a tetramer that consists of 2 pairs of globin chains (total of 4 chains per molecule). During the first few weeks of embryogenesis, hemoglobin is synthesized by the yolk sac and contains zeta or epsilon globin chains **(Choices G and F)**. Thereafter, one pair of the globin chains should always be alpha and the other should be non-alpha.

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Fetal hemoglobin (Hb F) production begins around 8 weeks gestation and replaces all embryonic hemoglobin by 14 weeks gestation, when erythropoiesis in the fetal liver and spleen is established. Hb F consists of 2 alpha and 2 gamma protein subunits (**α2γ2**). Production declines at birth, and Hb F comprises ~60-80% of all hemoglobin in a term newborn. Hb F is gradually replaced by adult hemoglobin (Hb A, α2β2) **(Choice A)** during the first 6 months of life, after which Hb A composes the vast majority of adult hemoglobin.

Compared to red blood cells with Hb A, those with Hb F have a **high oxygen affinity** as Hb F binds to 2,3-bisphosphoglycerate poorly. The greater affinity of Hb F facilitates transplacental oxygen delivery from the maternal circulation to that of the fetus.

(Choice C) Hemoglobin A2 (α2δ2) is a normal hemoglobin variant that makes up 2%-3% of hemoglobin in a healthy adult and is functionally similar to Hb A. Patients with beta-thalassemia major have impaired beta globin production, resulting in an excess of alpha globin chains (eg, Hb A2, Hb F) and no Hb A.

(Choices D and E) Alpha-thalassemia results from a shortage of alpha globin chains. Hemoglobin H (β4) and hemoglobin Barts (γ4) have a very high oxygen affinity and cannot release oxygen, resulting in tissue hypoxia. Hemoglobin H disease manifests as chronic hemolytic anemia. Hemoglobin Barts is incompatible with life (eg, hydrops fetalis) as normal fetal and adult hemoglobin cannot be produced.

Educational objective:
Hemoglobin F (Hb F) is the predominant hemoglobin type in the second and third trimesters of pregnancy and during the first few months after birth. Hb F consists of 2 alpha and 2 gamma protein subunits (α2γ2) and has a high affinity for oxygen, which facilitates oxygen transport across the placenta to the fetus. Hb A (α2β2) is the major hemoglobin in adults.

References

- Human embryonic, fetal, and adult hemoglobins have different subunit interface strengths. correlation with lifespan in the red cell.
- Advances in the understanding of haemoglobin switching.

Biochemistry Hematology & Oncology Fetal hemoglobin

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Biochemistry	Hematology & Oncology	Fetal hemoglobin
Subject	System	Topic

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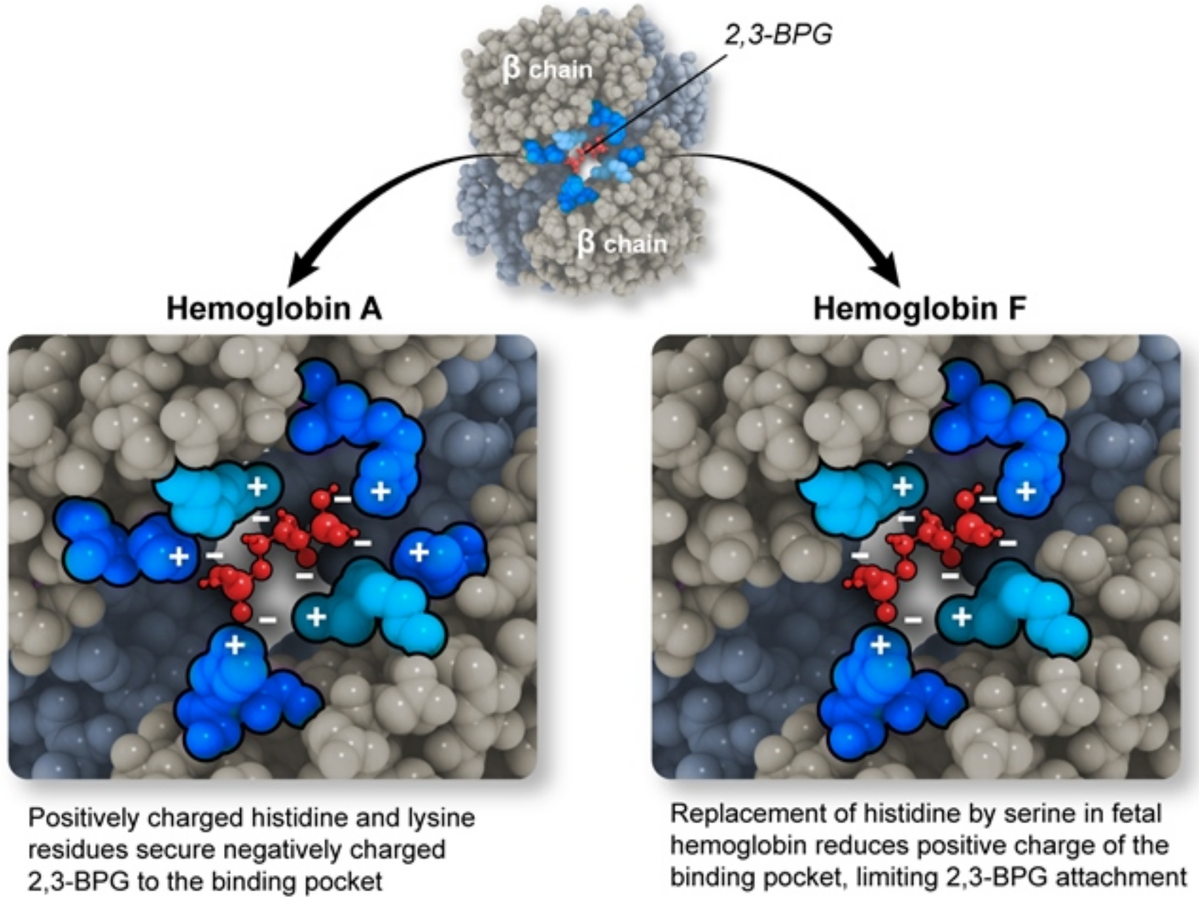
2,3-bisphosphoglycerate and hemoglobin binding



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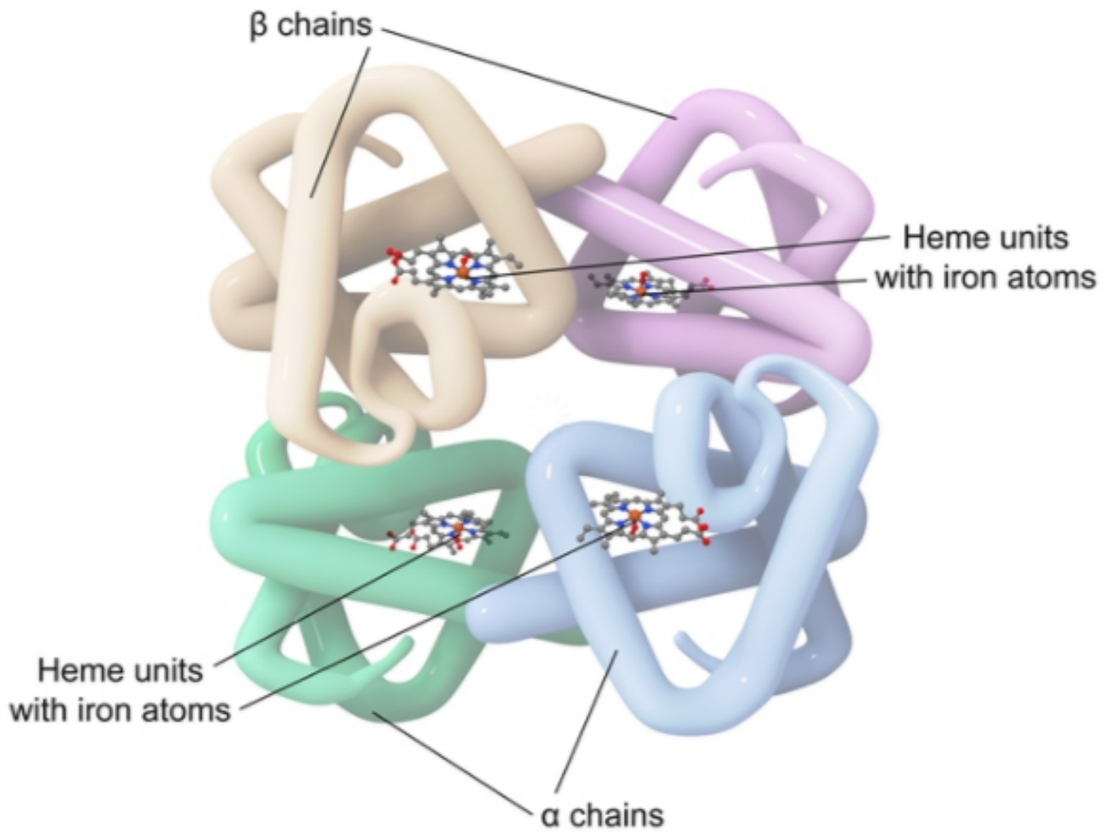
Hemoglobin tetramer



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Biochemistry Hematology & Oncology Fetal hemoglobin

A 34-year-old previously healthy man comes to the emergency department due to a 3-hour history of chest pain, diaphoresis, and dyspnea. He does not smoke, exercises regularly, and eats a balanced diet. His father died at age 56 from a myocardial infarction. His blood pressure is 110/70 mm Hg and pulse is 110/min and regular. Physical examination is unremarkable. ECG shows ST elevation in the anterolateral leads. Coronary angiogram reveals proximal left anterior descending artery stenosis and thrombosis, which is treated with angioplasty and stent placement. Laboratory results are as follows:

Total cholesterol	160 mg/dL	
Low-density lipoprotein	90 mg/dL	
Glucose, serum	98 mg/dL	
Homocysteine, plasma	21.5 μmol/L	(normal: 4-14 μmol/L)

Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

- A. Cystathionine
- B. Cysteine
- C. Methionine
- D. Methylmalonyl-CoA
- E. Succinyl-CoA

Submit

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Glucose, serum	98 mg/dL	
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Further testing reveals a homozygous mutation in the methylene tetrahydrofolate reductase gene that leads to decreased enzymatic activity. Due to this defect, the patient most likely has impairment converting homocysteine to which of the following?

- A. Cystathionine (9%)
- B. Cysteine (10%)
- ✓ C. Methionine (68%)
- D. Methylmalonyl-CoA (9%)
- E. Succinyl-CoA (2%)

Omitted
Correct answer

68%
Answered correctly

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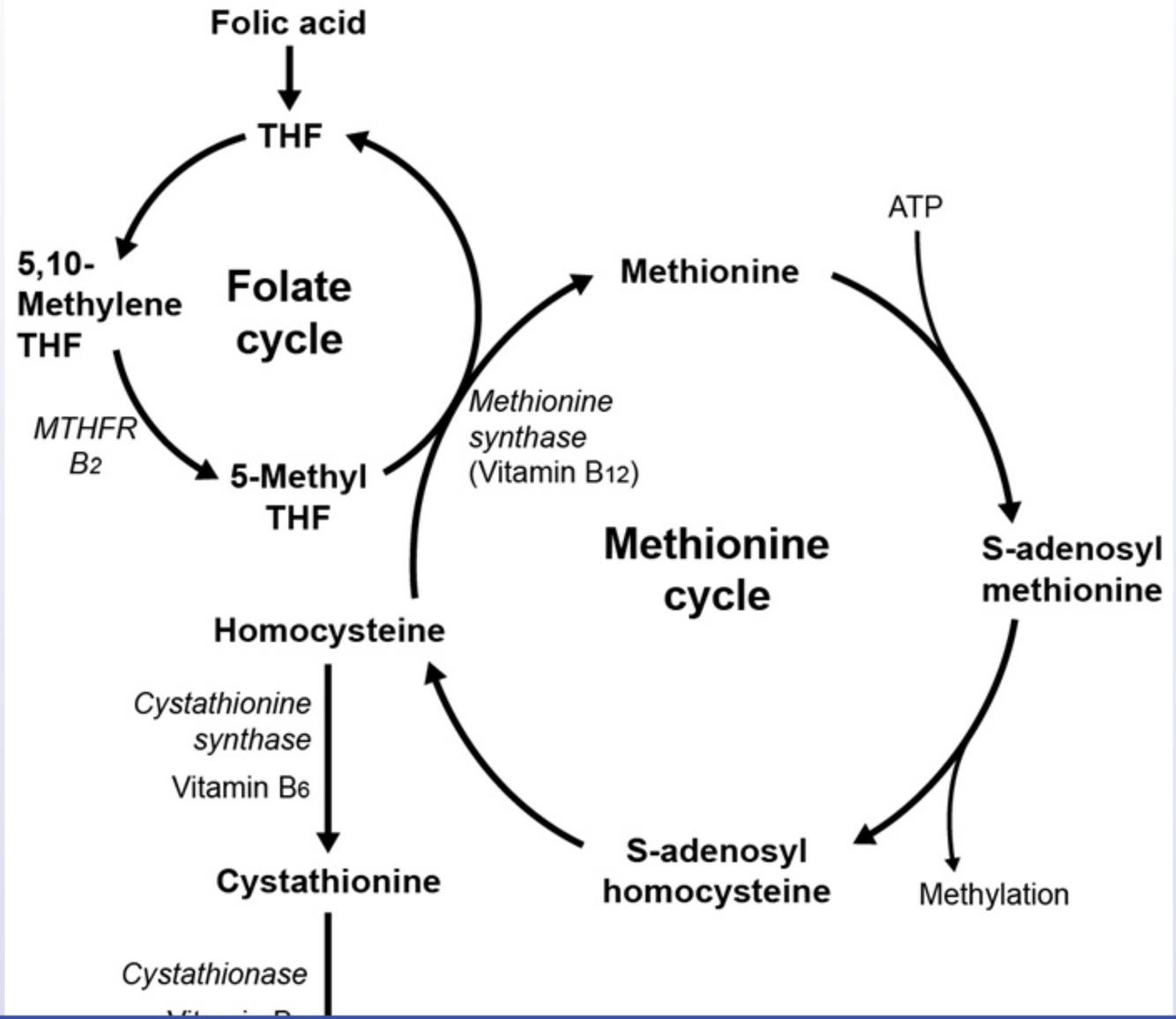
04/14/2020
Last Updated


Folic acid
THF
5,10-Methylene THF
Folate cycle
MTHFR
B2
5-Methyl THF
Methionine synthase
(Vitamin B12)
Methionine
ATP
Methionine cycle
S-adenosyl methionine
Homocysteine
Cystathionine synthase
Vitamin B6
Cystathionine
S-adenosyl homocysteine
Methylation
Cystathionase

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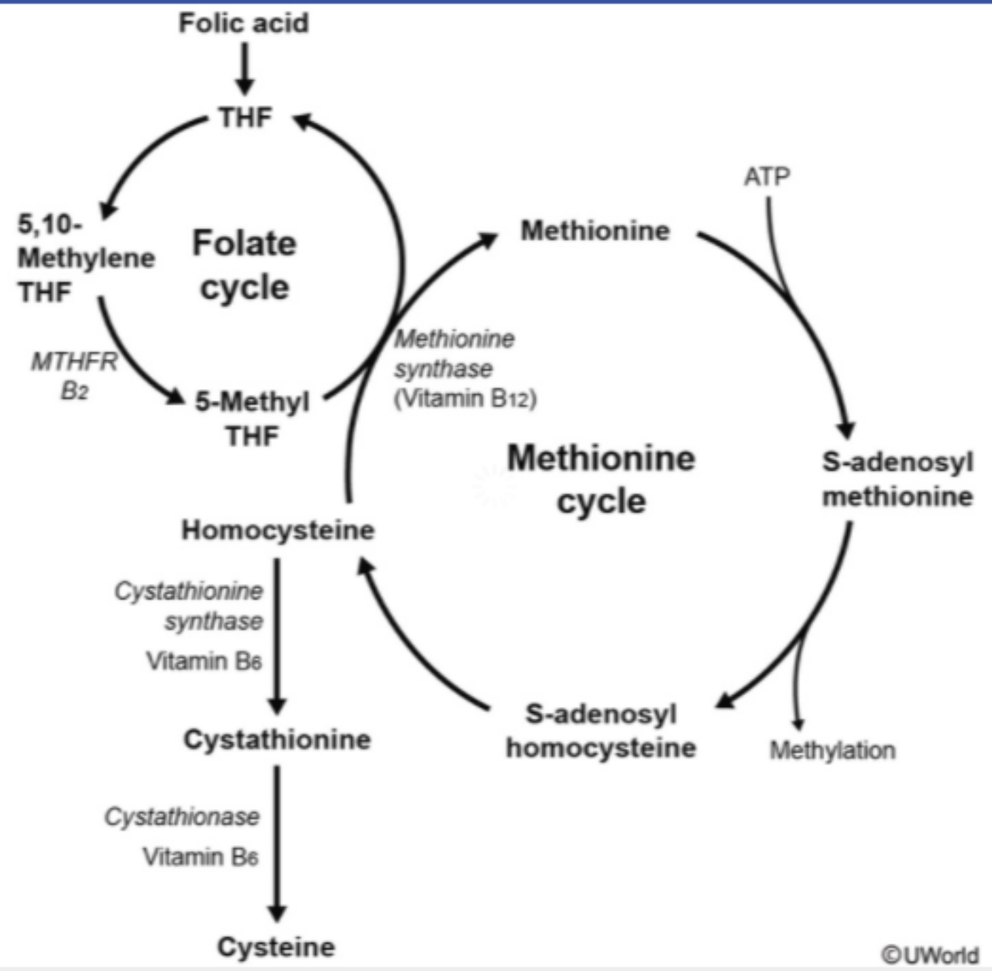

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Elevated levels of plasma homocysteine are an independent risk factor for **thrombotic events**, including venous thromboses, coronary artery disease, and ischemic stroke. The mechanism is thought to be due to direct and indirect induction of **endothelial damage**.

Homocysteine can be metabolized to **methionine** via remethylation or to **cystathionine** via transsulfuration. Remethylation to methionine occurs with the donation of a methyl group from methyl-tetrahydrofolate via **methionine synthase**, with vitamin B_{12} (cobalamin) as an important cofactor. Methyl-tetrahydrofolate is regenerated by the enzyme **methylene tetrahydrofolate reductase (MTHFR)**, using FAD as a cofactor. Homocysteine can also undergo transsulfuration via cystathionine-β-synthase to cystathionine **(Choice A)** and subsequently to cysteine **(Choice B)** via the enzyme cystathionase, using vitamin B_6 as a cofactor.

Elevations in plasma homocysteine can occur due to genetic mutations in critical enzymes and vitamin (cofactor) deficiencies. MTHFR deficiency is the most common genetic cause of hyperhomocysteinemia. Low levels of the B vitamins cobalamin, pyridoxine, and folate are associated with hyperhomocysteinemia. However, supplementation of B vitamins for patients with mildly to moderately elevated homocysteine levels has not demonstrated a decrease in cardiovascular risk or mortality.

(Choices D and E) Vitamin B_{12} is a cofactor for the enzyme methylmalonyl-CoA mutase in the conversion of methylmalonyl-CoA to succinyl-CoA, a reaction that occurs in the breakdown of odd-chain fatty acids and some amino acids. As a result, patients with vitamin B_{12} deficiency have elevated methylmalonyl-CoA levels that subsequently result in buildup of neurotoxic methylmalonic acid. Symptomatic consequences include lethargy, seizures, paresthesias, and hypotonia. Homocysteine is elevated in both folate and vitamin B_{12} deficiencies, but methylmalonyl-CoA is elevated in vitamin B_{12} deficiency only.

Educational objective:
Elevated levels of plasma homocysteine are an independent risk factor for thrombotic events. Homocysteine can be metabolized to methionine via remethylation or to cystathionine via transsulfuration. Hyperhomocysteinemia is most commonly due to genetic mutations in critical enzymes or deficiencies of vitamin B_{12}, vitamin B_6, and folate.

References

- Biochemistry of homocysteine in health and diseases.
- Homocysteine-lowering interventions for preventing cardiovascular events.
- Congenital MTHFR deficiency causing early-onset cerebral stroke in a case homozygous for MTHFR thermolabile variant.

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Biochemistry	Cardiovascular System	Homocysteine
Subject	System	Topic

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can also undergo transsulfuration via cystathionine-β-synthase to cystathionine **(Choice A)** and subsequently to cysteine **(Choice B)** via the

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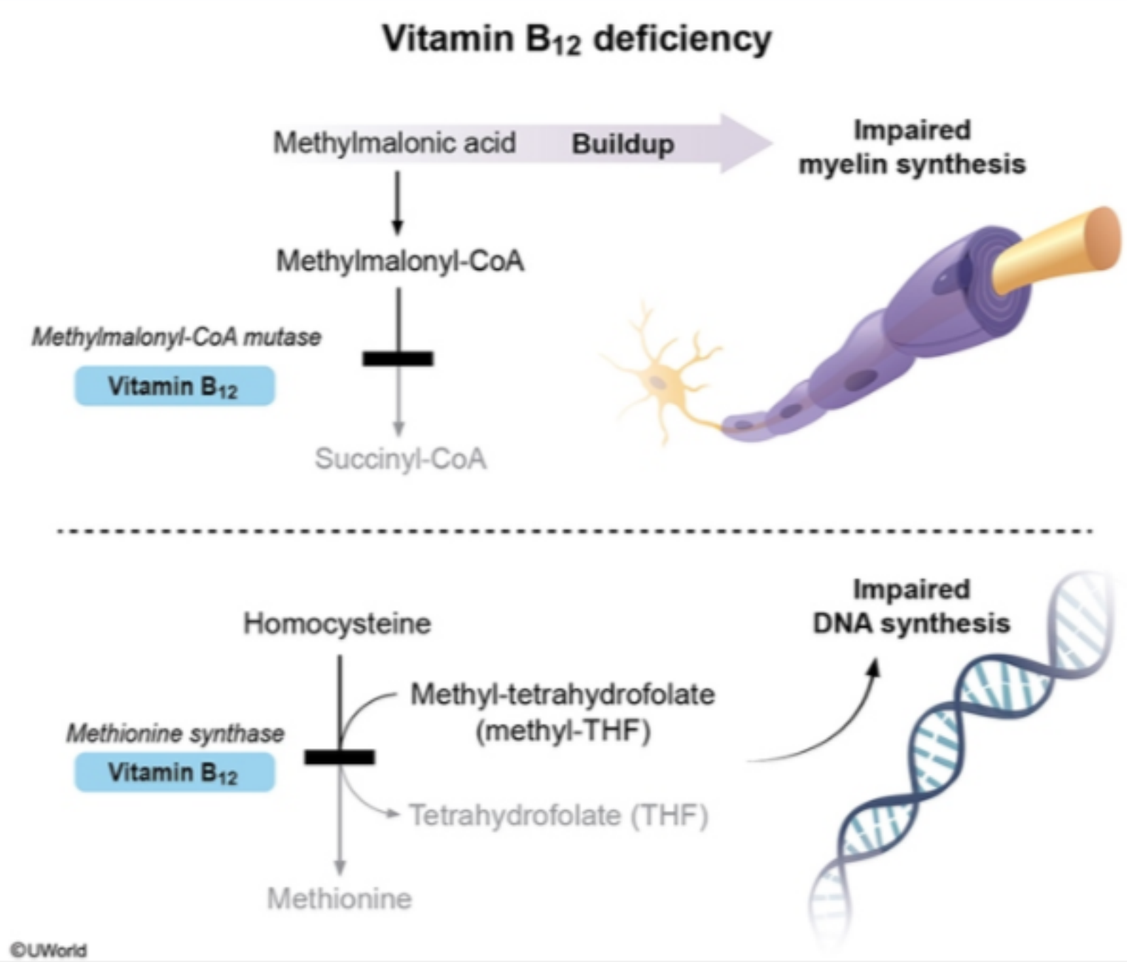

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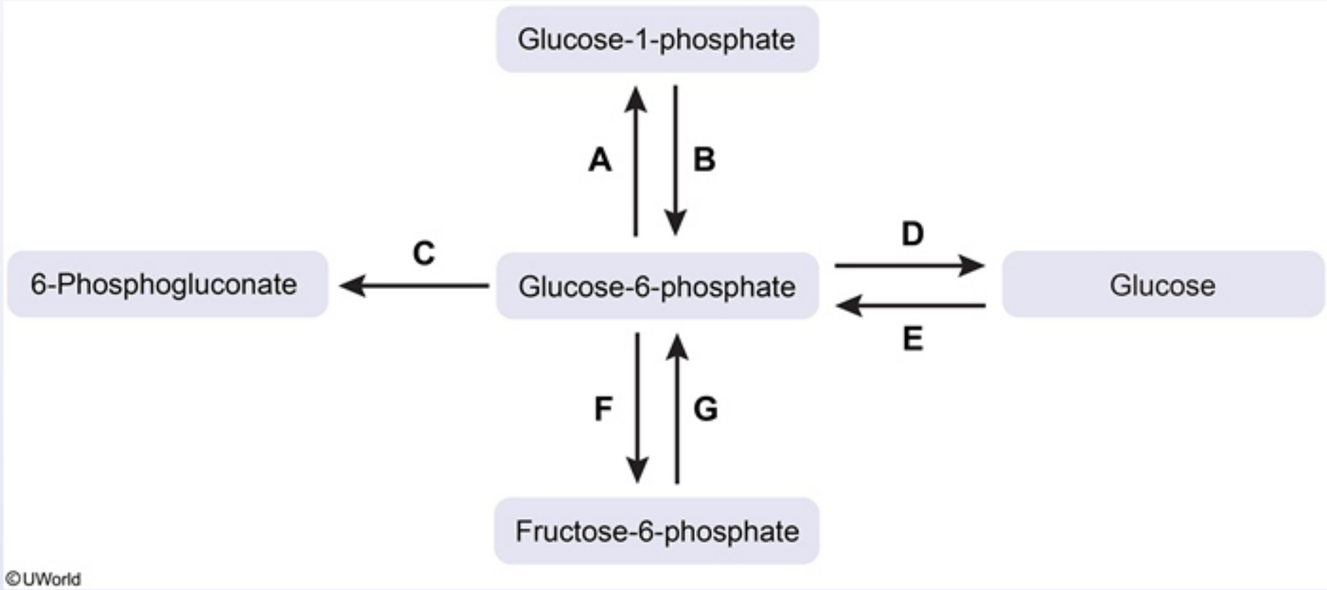
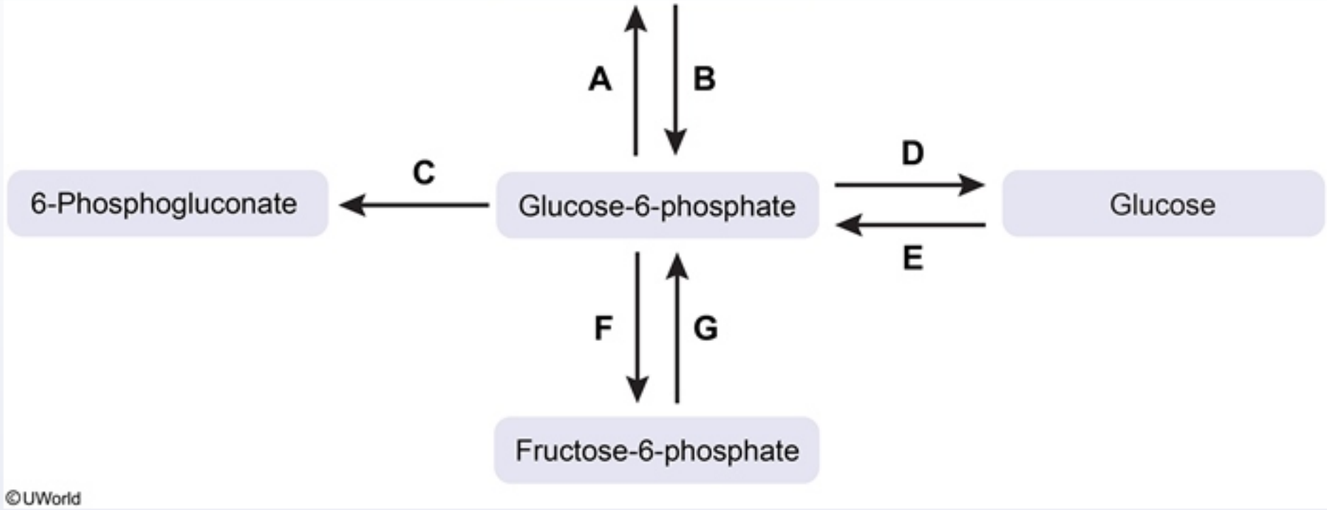
A 20-year-old man is evaluated in the emergency department for weakness, malaise, and dark urine. The patient was treated for a bacterial skin infection several days ago. Physical examination shows scleral icterus. Laboratory results reveal anemia with an elevated reticulocyte count. Abnormal erythrocytes are seen on peripheral smear. Which of the following substrate flow pathways is most likely deficient in this patient?



A. A
B. B
C. C
D. D
E. E
F. F



- A. A
- B. B
- C. C
- D. D
- E. E
- F. F
- G. G

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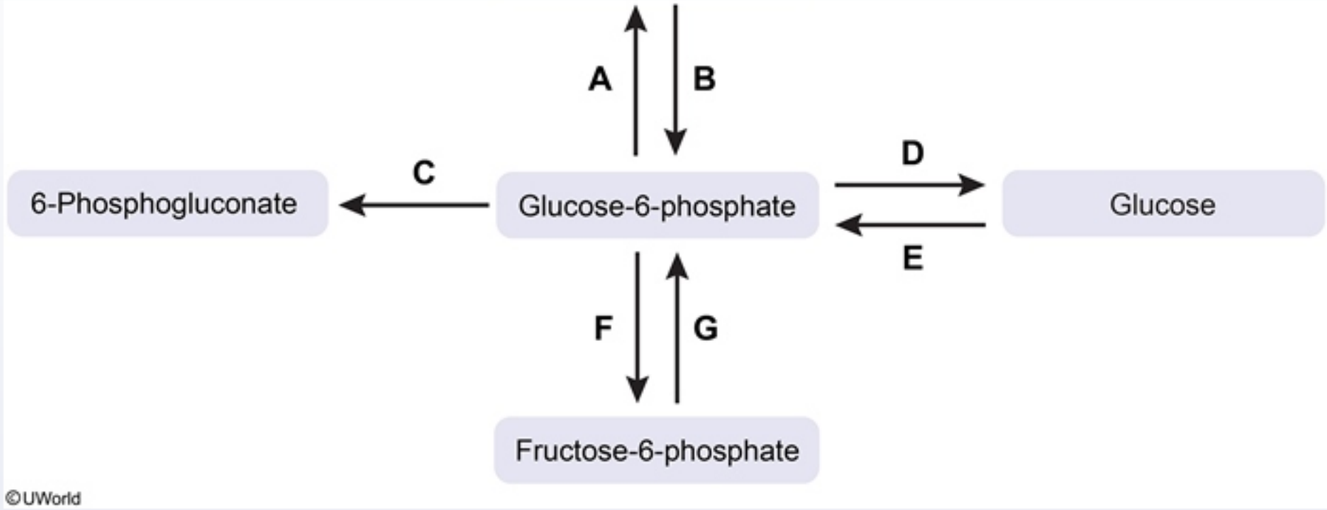


A. A (7%)
B. B (5%)
✓ C. C (57%)
D. D (11%)
E. E (5%)
F. F (9%)
G. G (2%)

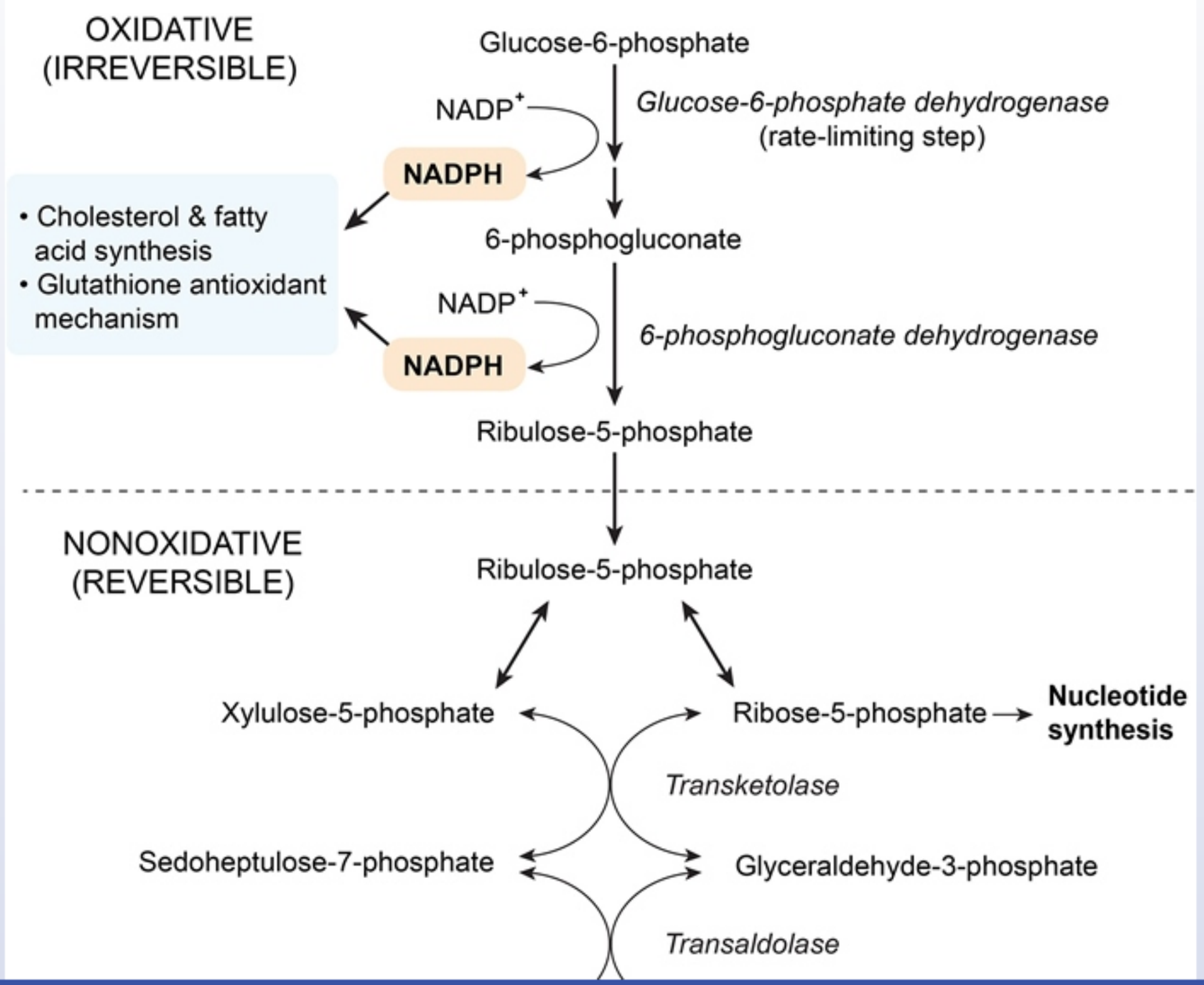
Omitted
Correct answer

57%
Answered correctly

05 secs
Time Spent

05/26/2020
Last Updated

Pentose phosphate pathway



Pentose phosphate pathway

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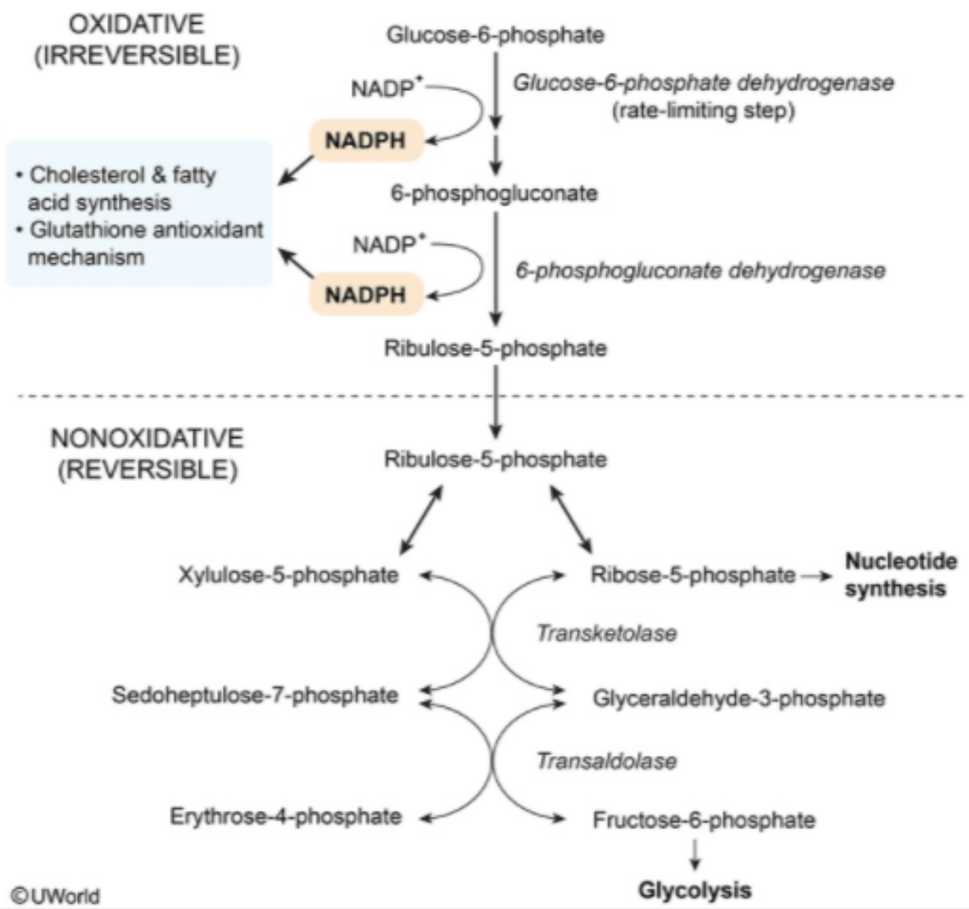

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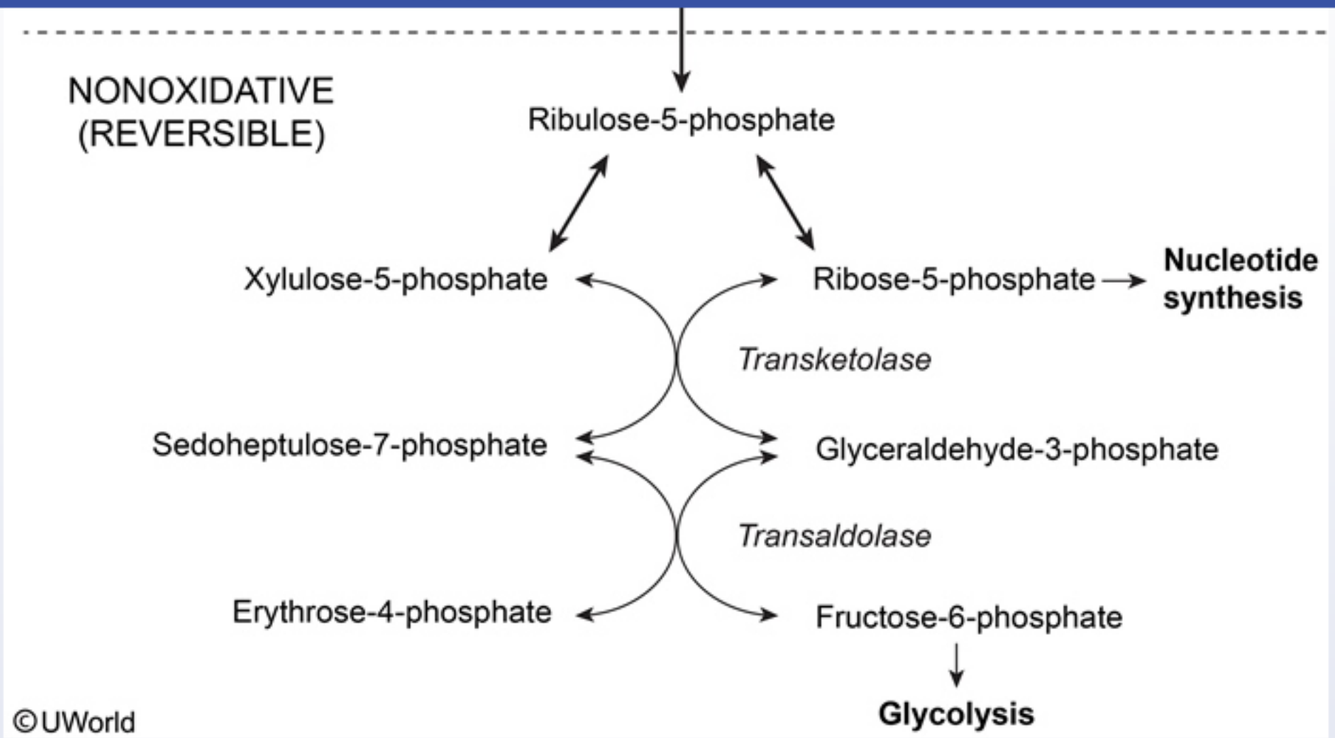

This patient is likely suffering from **glucose-6-phosphate dehydrogenase (G6PD)** deficiency, an X-linked recessive disorder resulting in episodic bouts of hemolysis when red blood cells experience increased oxidative stress.

G6PD is the rate-limiting enzyme of the **pentose phosphate pathway (PPP)**. This enzyme catalyzes the conversion of glucose-6-phosphate to 6-phosphogluconolactone, which is subsequently converted to 6-phosphogluconate. The PPP serves to generate both **NADPH** and **ribose-5-phosphate**, a precursor for nucleotide synthesis. Red blood cells utilize reduced NADPH to maintain a steady supply of **glutathione**, a molecule capable of neutralizing free radicals and therefore protecting the cells against oxidative damage. As the PPP is the only mechanism for red blood cells to generate NADPH, enzymatic defects in the pathway increase their susceptibility to oxidative damage.

Increased **oxidative stress** can occur as a result of exposure to medications (eg, antimalarials, sulfonamides), certain foods (eg, fava beans), and infection. This patient was likely treated with a sulfonamide drug for his bacterial skin infection, which precipitated hemolytic anemia. Oxidative

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Increased **oxidative stress** can occur as a result of exposure to medications (eg, antimalarials, sulfonamides), certain foods (eg, fava beans), and infection. This patient was likely treated with a sulfonamide drug for his bacterial skin infection, which precipitated hemolytic anemia. Oxidative damage to red blood cells also causes hemoglobin to denature, forming insoluble Heinz bodies that are removed in the spleen (produces characteristic **bite cells**).

(Choices A and B) Phosphoglucomutase interconverts glucose-6-phosphate and glucose-1-phosphate. This enzyme links glycogenolysis, glycogenesis, and glycolysis.

(Choice D) This reaction is the final step in both gluconeogenesis and glycogenolysis in the liver. It is catalyzed by glucose-6-phosphatase and results in the liberation of a free glucose molecule. Enzyme deficiency results in glycogen storage disease type I.

(Choice E) This reaction is the first step in glycolysis and is catalyzed by hexokinase or glucokinase. Hexokinase deficiency is a rare cause of hemolytic anemia, and glucokinase deficiency has been linked to hyperglycemic states and diabetes.

(Choices F and G) Interconversion of glucose-6-phosphate and fructose-6-phosphate is catalyzed by the bidirectional enzyme phosphoglucose isomerase. Enzyme deficiency is responsible for a small percentage of hemolytic anemias.

Educational objective:
Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme of the pentose phosphate pathway. G6PD deficiency is a common X-linked recessive disorder resulting in episodes of hemolytic anemia during times of increased oxidative stress (eg, use of

cells to generate NADPH, enzymatic defects in the pathway increase their susceptibility to oxidative damage.

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Glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme of the pentose phosphate pathway. G6PD deficiency is a common X-linked recessive disorder resulting in episodes of hemolytic anemia during times of increased oxidative stress (eg, use of antimalarials/sulfonamide, infections).

References

- Glucose-6-phosphate dehydrogenase deficiency.

Biochemistry	Hematology & Oncology	G6PD deficiency
Subject	System	Topic

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In an animal experiment, mice proerythroblasts are cultured in 2 different growth media; the first medium is folate deficient, whereas the second (control) is supplemented with folic acid. Both media contain high concentrations of erythropoietin. Over 48 hours, cells in the control media proliferate and differentiate into reticulocytes, whereas in the folate-deficient media, cell proliferation is minimal, with the majority of cells undergoing apoptosis. In another experiment, a substance is added to the folate-deficient media, which prevents apoptosis and permits proliferation of the proerythroblasts. Which of the following is the most likely substance added to the growth medium?

- A. Cobalamin
- B. Cytosine
- C. Glutamine
- D. Homocysteine
- E. Thymidine

Submit

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- A. Cobalamin (33%)
- B. Cytosine (3%)
- C. Glutamine (3%)
- D. Homocysteine (17%)
- ✓ E. Thymidine (41%)

Omitted
Correct answer
E

41%
Answered correctly

02 secs
Time Spent

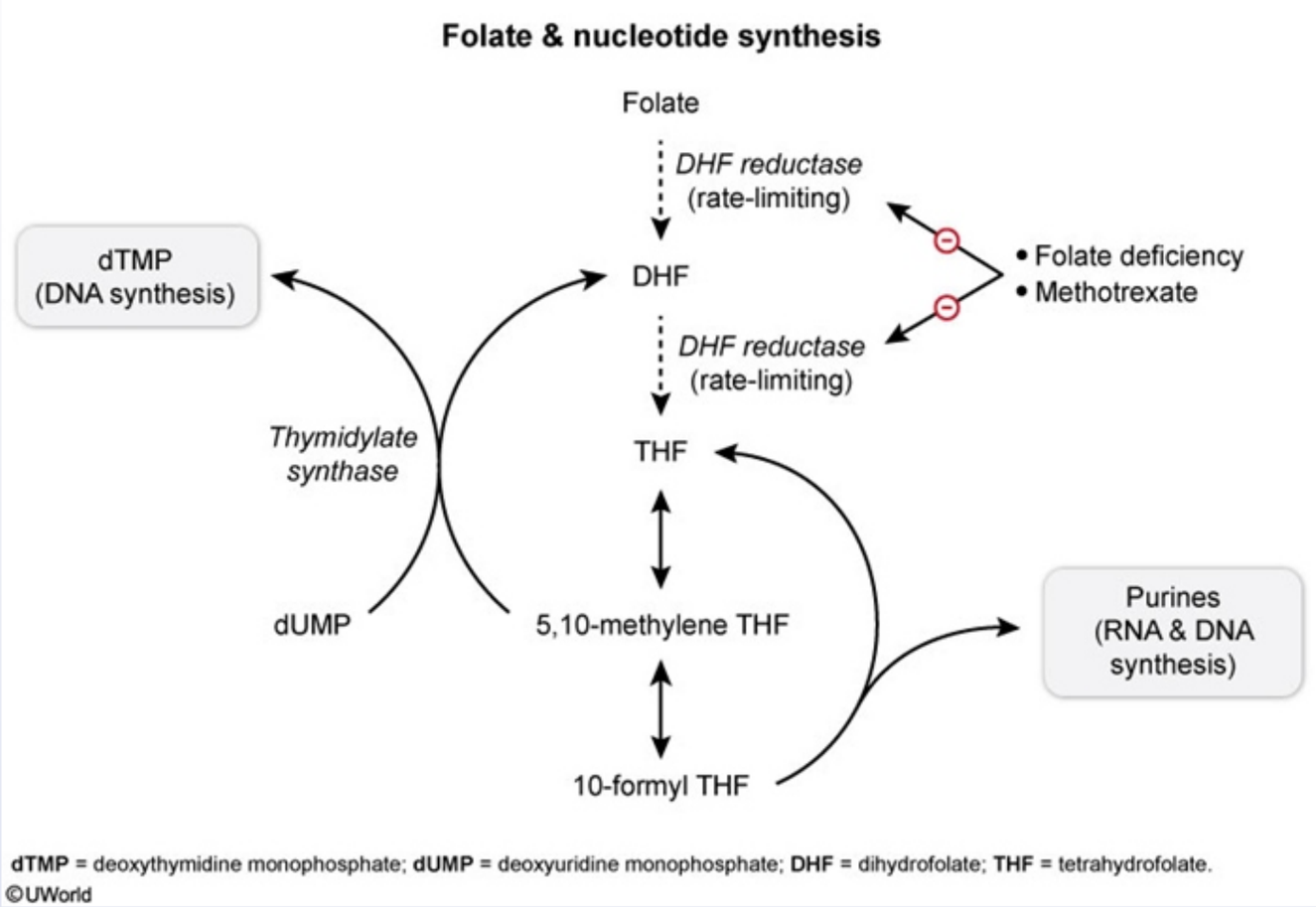
01/18/2020
Last Updated

Explanation

Folate & nucleotide synthesis

Folate

DHF reductase



Folate derivatives are crucial in the synthesis of nucleic acids (particularly thymine, but also purine bases), conversion of homocystine to methionine, and generation of one-carbon carriers (eg, S-adenosylmethionine) for methylation reactions. All biochemical functions of folate require the reduced **tetrahydrofolate** form of the vitamin, which is synthesized by dihydrofolate reductase (a rate-limiting step in folate metabolism).

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The enzyme **thymidylate synthase** is responsible for converting deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (**dTMP**]). Although most enzymes involved in one-carbon metabolism maintain folate in its active tetrahydrofolate form, thymidylate synthase is unique in that it oxidizes 5,10-methylenetetrahydrofolate to **dihydrofolate**. This makes de novo thymidine synthesis particularly susceptible to folate-deficient conditions, as tetrahydrofolate must be continuously regenerated by dihydrofolate reductase.

In this experiment, inhibition of thymidylate synthase due to low folate conditions increases the ratio of dUMP to dTMP, causing the incorporation of uracil into DNA in place of thymidine. This leads to excessive activation of DNA repair mechanisms, resulting in double-stranded DNA breaks and apoptosis. Thymidine supplementation increases the amount of available thymidine and is capable of inhibiting apoptosis in folate-deficient cells.

(Choice A) Cobalamin is a necessary cofactor for methionine synthase, the enzyme that transfers a methyl group from 5-methyltetrahydrofolate to homocysteine, forming methionine and regenerating tetrahydrofolate. Cobalamin deficiency can cause folate to become trapped in 5-methyltetrahydrofolate form, resulting in secondary folate deficiency. However, cobalamin supplementation would not be of significant benefit in this patient as the primary folate deficiency prevents synthesis of tetrahydrofolate in the first place.

(Choice B) Cytosine is a pyrimidine base. Unlike thymine, it is not dependent on folate and can be synthesized in sufficient quantities under folate-deficient conditions.

(Choice C) Glutamine is a major source of nitrogen in the synthesis of purine and pyrimidine bases. However, glutamine supplementation would not ameliorate the cellular apoptosis induced by folate deficiency.

(Choice D) Homocysteine is an amino acid associated with endothelial cell injury and vascular inflammation. Levels are elevated in folate deficiency due to impaired conversion into methionine.

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References

- Apoptosis mediates and thymidine prevents erythroblast destruction in folate deficiency anemia.

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Biochemistry	Hematology & Oncology	Folic acid deficiency
Subject	System	Topic

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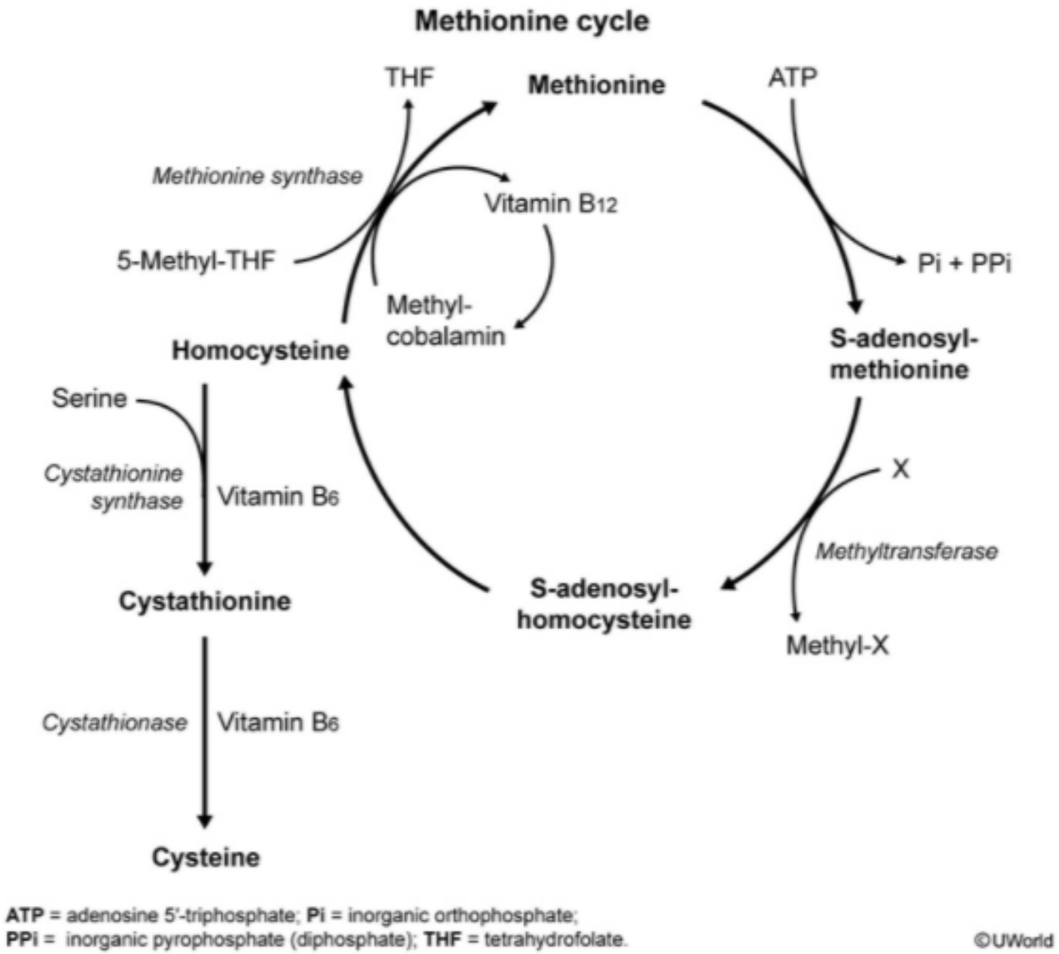
Exhibit Display



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A 2-year-old boy is evaluated for easy bruising. His parents report that he develops marked bruising and open wounds following minor trauma. The skin is difficult to suture due to its extreme fragility. Physical examination reveals hyperextensible skin, multiple ecchymoses over the forearms and pretibial regions, and an umbilical hernia. A skin biopsy is performed, and histochemical evaluation of the biopsy reveals a defect in extracellular processing of collagen. Which of the following steps of collagen synthesis is most likely impaired in this patient?

A. Glycosylation of hydroxylysine residues

B. Interchain C-terminal disulfide bond formation

C. N-terminal propeptide removal

D. Proline residue hydroxylation

E. Triple helix formation

Submit

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- A. Glycosylation of hydroxylysine residues (10%)
- B. Interchain C-terminal disulfide bond formation (18%)
- ✓ C. N-terminal propeptide removal (23%)
- D. Proline residue hydroxylation (17%)
- E. Triple helix formation (29%)

Omitted
Correct answer
C

23%
Answered correctly

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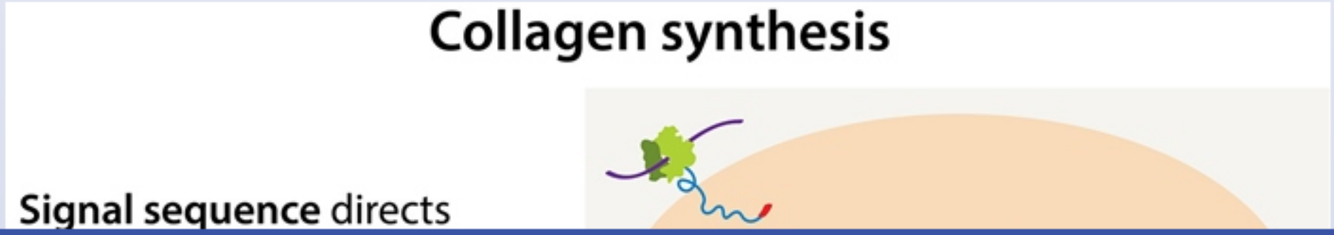
Time Spent

06/15/2020
Last Updated

Explanation



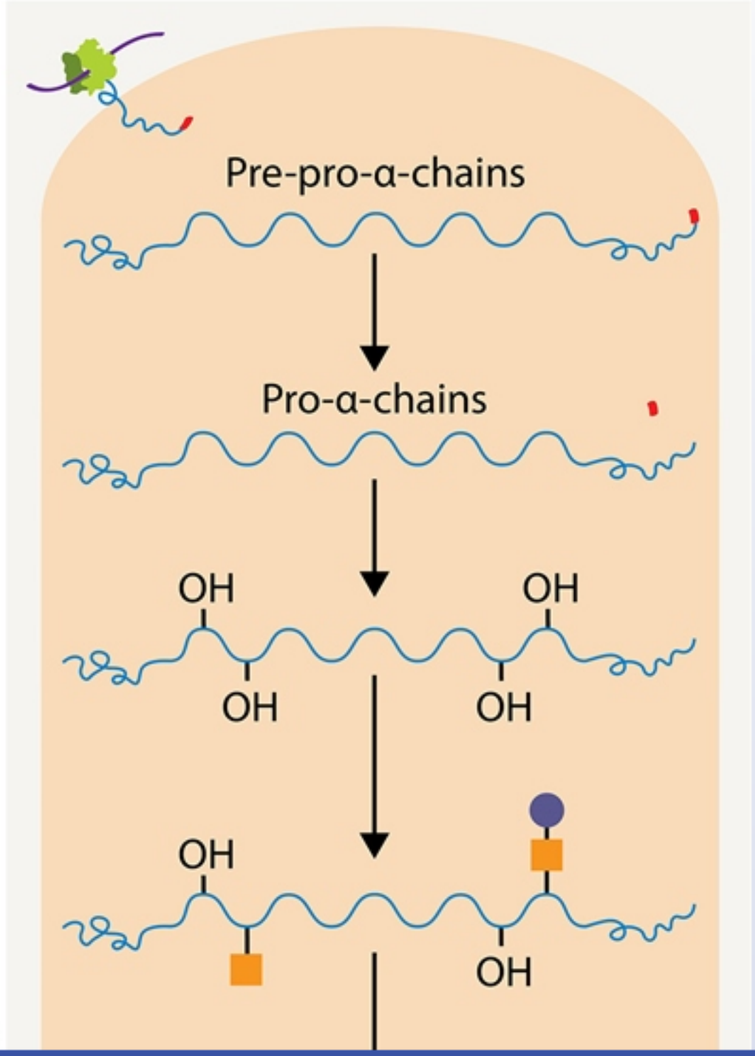
Collagen synthesis

Signal sequence directs growing polypeptide chain into endoplasmic reticulum

Signal sequence is cleaved

Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**

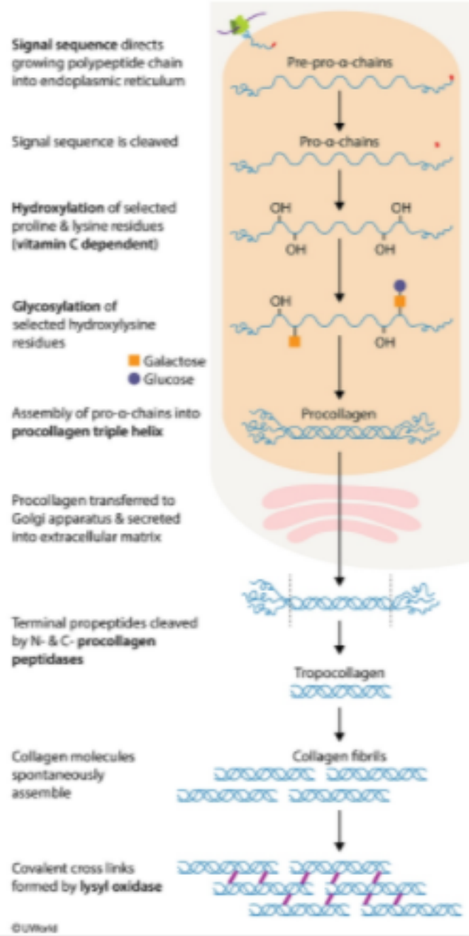
Glycosylation of selected hydroxylysine residues



Galactose

Exhibit Display

Collagen synthesis



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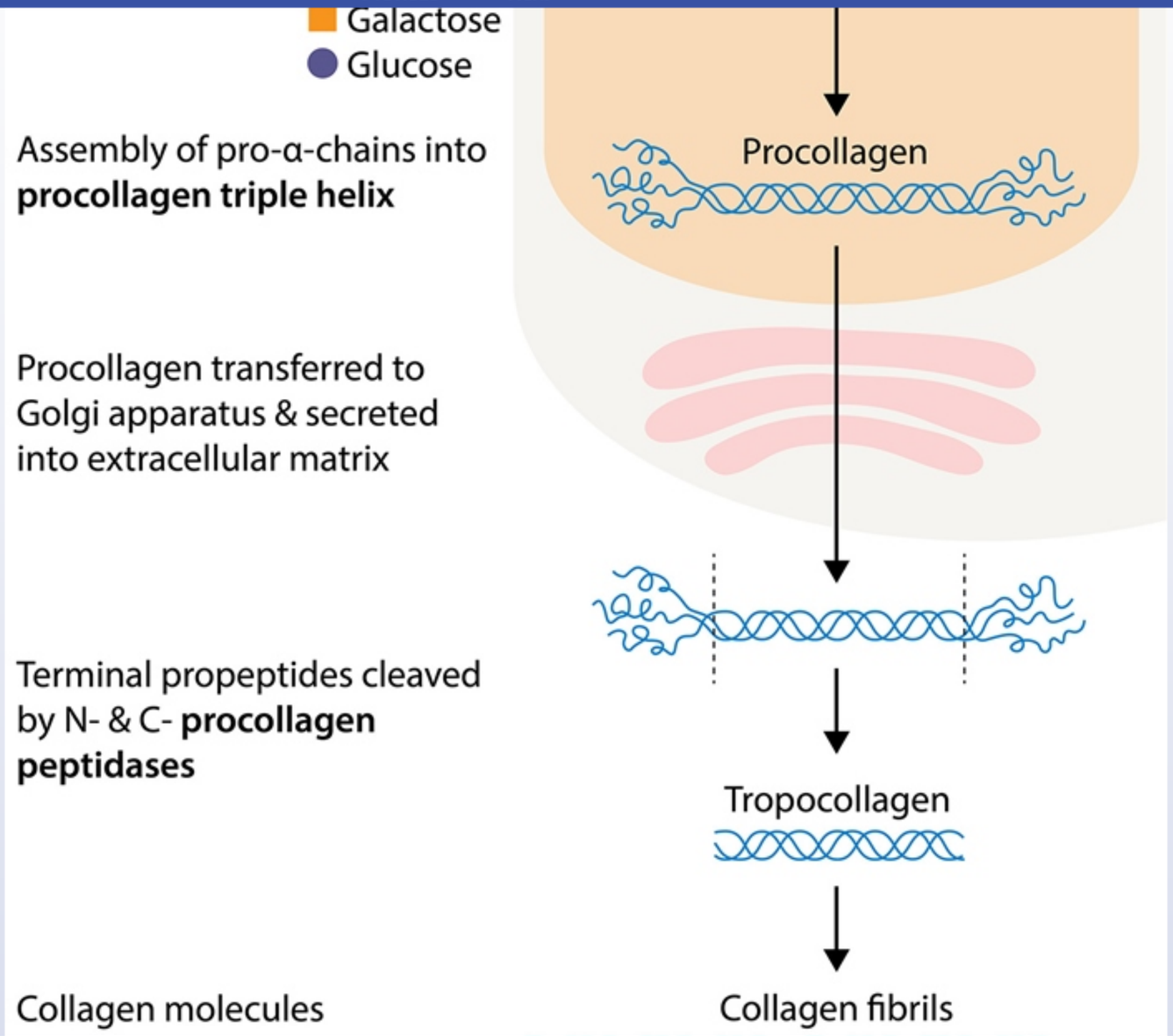
Galactose


Galactose
Glucose
Assembly of pro-α-chains into **procollagen triple helix**
Procollagen
Procollagen transferred to Golgi apparatus & secreted into extracellular matrix
Terminal propeptides cleaved by N- & C- **procollagen peptidases**
Tropocollagen
Collagen molecules
Collagen fibrils

This child likely has **Ehlers-Danlos syndrome**, a group of rare hereditary disorders characterized by **defective collagen synthesis**. The condition can be caused by a **deficiency** in **procollagen peptidase**, the enzyme that cleaves terminal propeptides from procollagen in the extracellular space. Impaired propeptide removal results in the formation of soluble collagen that does not properly crosslink. Consequently, patients often have joint laxity, **hyperextensible skin, fragile tissue** with easy bruising, and poor wound healing.

Each collagen molecule consists of 3 polypeptide α-chains held together by hydrogen bonds, forming a triple helix. Collagen assumes this conformation because each of the α-chains has a simple, repetitive amino acid sequence represented as $(Gly\text{-}X\text{-}Y)_n$. The smallest amino acid, glycine (Gly), is necessary at every third position to ensure compact coiling of the helix. Many of the amino acids represented by X and Y are proline residues, which kink the polypeptide chain and enhance the rigidity of the helical structure due to their ring configuration.

Mature collagen is synthesized by fibroblasts, osteoblasts, and chondroblasts through the following steps:

1. As translation begins in the cytoplasm, an amino acid signal sequence at the N-terminus of the α-chain facilitates ribosomal binding to the rough endoplasmic reticulum (RER) and passage of the growing polypeptide chain (pre-pro-α-chain) into the RER.
2. Inside the RER, the hydrophobic signal sequence is cleaved to yield the pro-α-chain. Proline and lysine at the Y positions of the pro-α-chain are hydroxylated to hydroxyproline and hydroxylysine, respectively **(Choice D)**. Glycosylation of select hydroxylysine residues also occurs within the RER **(Choice A)**.
3. The central helical region of the pro-α-chain is flanked by N- and C-terminal propeptides. Disulfide bond formation between the C-terminal propeptide region of 3 α-chains brings the chains into an alignment favorable for assembly into a triple helix (procollagen molecule) **(Choices B and E)**.
4. Procollagen molecules are then transported through the Golgi apparatus into the extracellular space. The N- and C-terminal propeptides are cleaved by procollagen peptidases, converting procollagen into less soluble tropocollagen.
5. Tropocollagen monomers self-assemble into collagen fibrils. Finally, lysyl oxidase helps create covalent crosslinks between collagen fibrils to form strong collagen fibers.

Educational objective:
Ehlers-Danlos syndrome is a group of rare hereditary disorders characterized by defective collagen synthesis. It can be caused by procollagen

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Educational objective:

Ehlers-Danlos syndrome is a group of rare hereditary disorders characterized by defective collagen synthesis. It can be caused by procollagen peptidase deficiency, which results in impaired cleavage of terminal propeptides in the extracellular space. Patients often have joint laxity, hyperextensible skin, and tissue fragility due to the formation of soluble collagen that does not properly crosslink.

References

- Defect in conversion of procollagen to collagen in a form of Ehlers-Danlos syndrome.
- Defects in the biochemistry of collagen in diseases of connective tissue.
- Clinical and genetic aspects of Ehlers-Danlos syndrome, classic type.

Biochemistry	Dermatology	Ehlers danlos syndrome
Subject	System	Topic

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A 7-year-old African American boy is brought to the office by his parents. The parents state that the boy has been hospitalized several times for severe pains in his back and extremities. The patient is very active when he is not in pain but gets quite tired by the end of the day. He has no other medical problems and takes no medications except acetaminophen for pain control. On examination, the conjunctivae are pale. Blood count reveals a hemoglobin level of 7.8 mg/dL and a reticulocyte count of 15%. A valine for glutamic acid substitution at position 6 of the β globin chain of the hemoglobin molecule is suspected. This patient's hemoglobin would most likely aggregate upon which of the following?

- A. 2,3-bisphosphoglycerate depletion
- B. β globin chain folding
- C. Capillary pH values >7.4
- D. Interaction with fetal hemoglobin
- E. Oxygen unloading

Submit

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A. 2,3-bisphosphoglycerate depletion (11%)
B. β globin chain folding (9%)
C. Capillary pH values >7.4 (5%)
D. Interaction with fetal hemoglobin (4%)
✓ E. Oxygen unloading (68%)

Omitted
Correct answer
E

68%
Answered correctly

02 secs
Time Spent

06/20/2020
Last Updated

Explanation

In **sickle cell (hemoglobin S [HbS]) anemia**, the nonpolar amino acid valine replaces the charged amino acid glutamate at position 6 of the β globin chain. This results in the alteration of a hydrophobic portion of the β globin chain that fits into a complementary site on the α globin chain of another hemoglobin molecule. As a result, hemoglobin molecules aggregate under anoxic conditions. After polymerization, HbS initially forms a gel and then a meshwork of fibrous polymers causing the red blood cells to distort into an abnormal sickle shape.

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Sickling is promoted by conditions associated with **low oxygen** levels, increased acidity, or low blood volume (dehydration). Sickled cells are not flexible enough to pass through microvasculature. As a result, they impede blood flow and cause microinfarcts in tissues and painful vasoocclusive crises. Organs in which blood moves slowly (eg, spleen, liver) are predisposed to lower oxygen levels or acidity. Organs with particularly high metabolic demands (eg, brain, muscles, placenta) promote sickling by extracting more oxygen from the blood (**oxygen unloading**). The sickling process is complex and incompletely understood.

(Choices A and C) The molecule 2,3-bisphosphoglycerate (2,3-BPG) binds the 2 β globin chains ionically and stabilizes the taut (T) deoxyhemoglobin. This binding decreases hemoglobin's oxygen affinity, facilitating oxygen release at the tissue level. With 2,3-BPG depletion, hemoglobin affinity for oxygen increases (left shift on oxygen-hemoglobin dissociation curve), and this results in oxygen uptake by hemoglobin; therefore, erythrocyte sickling will decrease. Similarly, increased acidity or low pH is associated with sickling, so decreased acidity with elevated capillary pH values >7.4 would not promote sickling.

(Choice B) The globin chains in the hemoglobin tetramer are folded compactly, with nonpolar hydrophobic residues in the interior and charged polar residues on the surface. A valine for glutamic acid substitution does not result in a significant change in β globin folding. It is the mature hemoglobin tetramer that undergoes polymerization, not individual globin chains during folding.

(Choice D) HbS does not polymerize when fetal hemoglobin (HbF) is present, so patients with sickle cell anemia often do not have symptoms until the HbF fraction decreases a few months after delivery. Some patients with HbS may have fewer clinical manifestations because they produce larger amounts of HbF as adults.

Educational objective:
Hemoglobin S (HbS) aggregates in the deoxygenated state. HbS polymers form fibrous strands that reduce red blood cell membrane flexibility and promote sickling. Sickling occurs under conditions associated with anoxia including low pH and high levels of 2,3-bisphosphoglycerate. These inflexible erythrocytes predispose to microvascular occlusion and microinfarcts.

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References

- Newer aspects of the pathophysiology of sickle cell disease vaso-occlusion.
- Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches.

Biochemistry	Hematology & Oncology	Sickle cell
Subject	System	Topic

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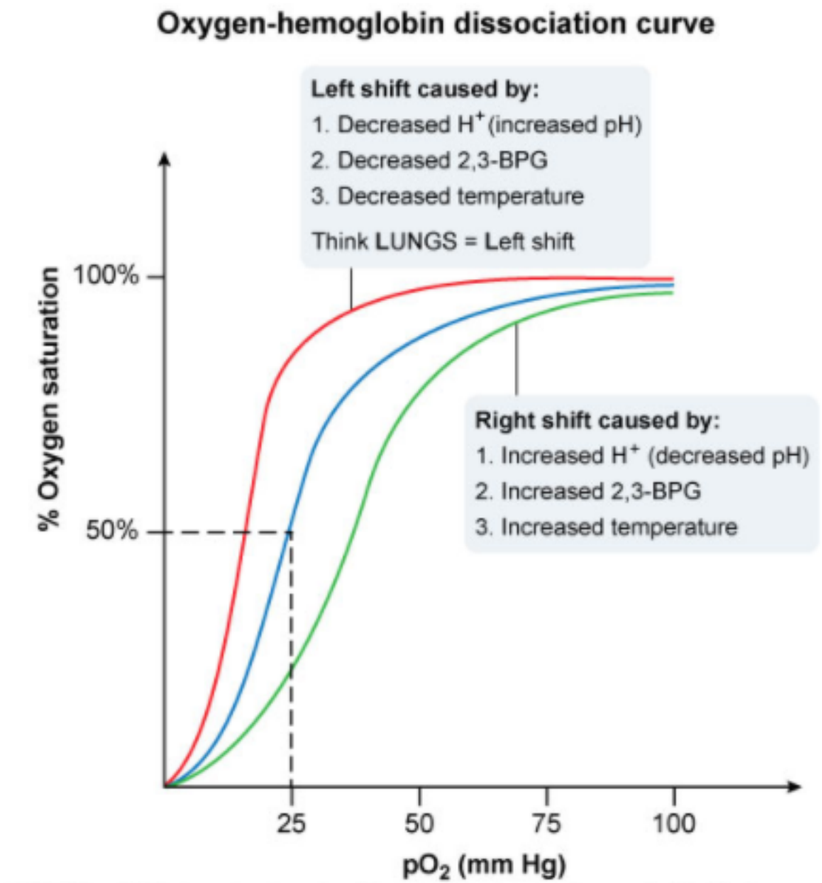
Exhibit Display



2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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Researchers studying chronic lymphocytic leukemia (CLL) observe that in some patients the disease is indolent, with limited growth over more than a decade, whereas in other patients the disease is more aggressive and becomes symptomatic early on. They find that genetic abnormalities can be detected in a majority of patients with CLL and may play a role in determining the difference between the 2 disease courses. A clinical study is conducted with the hypothesis that individuals with CLL with trisomy of chromosome 12 have a more favorable course than individuals with other genetic changes. Which of the following laboratory techniques would be most useful for identifying patients with this genetic abnormality?

A. Enzyme-linked immunosorbent assay
B. Flow cytometry
C. Fluorescence in situ hybridization
D. Northern blotting
E. Western blotting

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Researchers studying chronic lymphocytic leukemia (CLL) observe that in some patients the disease is indolent, with limited growth over more than a decade, whereas in other patients the disease is more aggressive and becomes symptomatic early on. They find that genetic abnormalities can be detected in a majority of patients with CLL and may play a role in determining the difference between the 2 disease courses. A clinical study is conducted with the hypothesis that individuals with CLL with trisomy of chromosome 12 have a more favorable course than individuals with other genetic changes. Which of the following laboratory techniques would be most useful for identifying patients with this genetic abnormality?

- A. Enzyme-linked immunosorbent assay (2%)
- B. Flow cytometry (6%)
- ✓ C. Fluorescence in situ hybridization (84%)
- D. Northern blotting (4%)
- E. Western blotting (2%)

Omitted
Correct answer
C

84%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Malignant cells typically contain a number of chromosomal translocations, deletions, or duplications that result in deregulation of gene expression and production of novel fusion proteins. **Cytogenic analysis** of tumor cells often demonstrates characteristic chromosomal abnormalities that may aid diagnosis, treatment selection, and estimation of prognosis.

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Fluorescence in situ hybridization (FISH) is a highly sensitive cytogenetic test that can identify the presence of **chromosomal duplications** and **large deletions and translocations**. FISH probes are single-stranded DNA segments that are a few hundred kilobases in length; they are added to the cell of interest and anneal to complementary regions of the cell chromosome, which allows the area of interest to be identified visually.

FISH is far more sensitive than traditional karyotyping (chromosome banding) and can be applied to both dividing (metaphase) and nondividing (interphase) cells. It is often used to identify large structural chromosomal abnormalities such as the *BCR-ABL1* fusion of t(9;22) in chronic myeloid leukemia. However, small chromosomal insertions and deletions cannot be identified by FISH (because the probe size is somewhat large), and chromosomal inversions will be missed because FISH can only identify the presence or absence of a chromosomal segment, not the order in which it is coded.

(Choice A) Enzyme-linked immunosorbent assay (ELISA) is used to quantify antibodies or antigens in a fluid.

(Choice B) Flow cytometry is often used in the diagnosis of leukemia. However, this laser-based test evaluates surface markers (eg, CD5) on individual cells, not chromosomal duplications.

(Choice D) Northern blotting is a technique that size-fractionates RNA in a gel and then targets a specific mRNA sequence of interest. It can determine the quantity and size of a particular mRNA section.

(Choice E) Western blotting is a technique that size-fractionates proteins in a gel and then targets a specific protein using an antibody with a radiotracer/enzyme. It is often used to confirm a positive ELISA test in the setting of HIV or Lyme disease infection.

Educational objective:
Fluorescence in situ hybridization (FISH) can identify specific chromosomal translocations, duplications, or deletions using a single-stranded, complementary DNA segment that is tagged with a radiotracer. FISH is rapid, highly sensitive and specific, and can be used on tissues with low mitotic rates. However, the targeted chromosomal abnormality must be somewhat large in order to be identified.

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Biochemistry	Hematology & Oncology	Laboratory techniques
Subject	System	Topic

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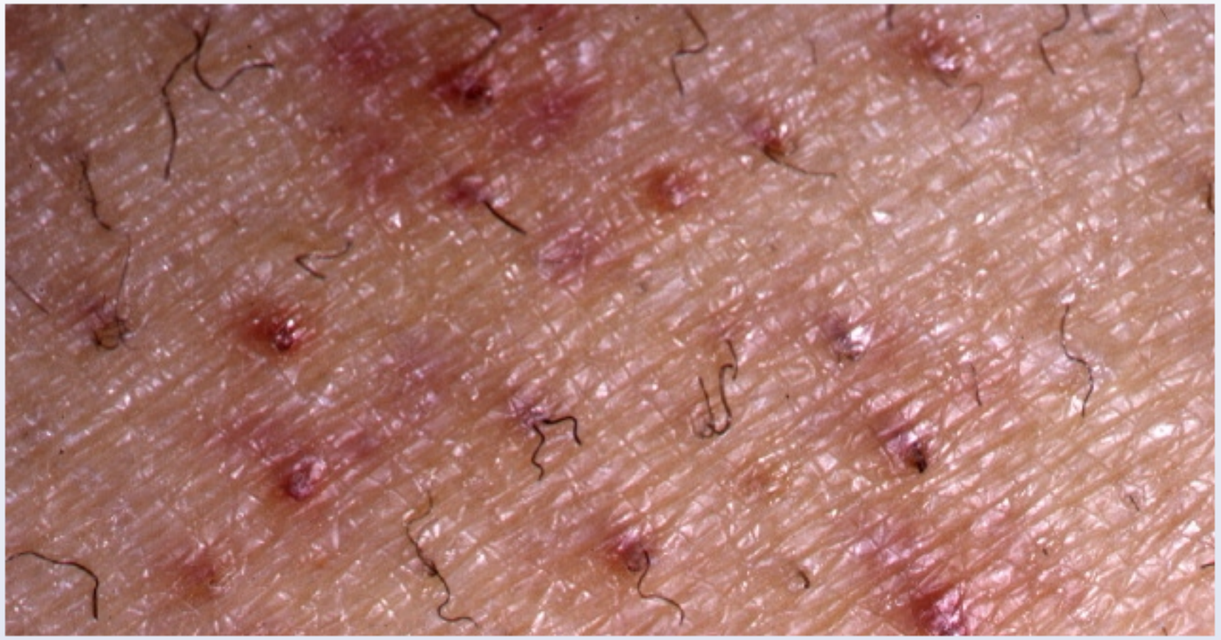
A 78-year-old woman comes to the office due to tenderness and easy bleeding of the gums when she brushes her teeth. The patient has brushed her teeth twice a day for as long as she can remember and has not experienced these symptoms before. Physical examination shows swollen gingiva that bleed on probing. Her skin findings are shown in the image below.



Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused

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Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

- A. Extracellular space
- B. Golgi apparatus
- C. Lysosomes
- D. Mitochondria
- E. Nucleus
- F. Rough endoplasmic reticulum

Submit

Further questioning reveals that the patient lives alone and that her diet consists primarily of tea and toast. Her symptoms are most likely caused by hypoactivity of an enzyme found in which of the following compartments?

- A. Extracellular space (15%)
- B. Golgi apparatus (14%)
- C. Lysosomes (4%)
- D. Mitochondria (10%)
- E. Nucleus (3%)
- ✓ F. Rough endoplasmic reticulum (50%)

Omitted
Correct answer

50%
Answered correctly

05 secs
Time Spent

06/16/2020
Last Updated

Explanation

Disorders caused by defective collagen synthesis		
Disorder	**Defining characteristics**	**Impairment**
Ehlers-Danlos syndrome (types I & II)	• Joint hypermobility • Hyperextensible, fragile skin • Most common form of EDS	Mutation in type V collagen
Osteogenesis imperfecta	• Spontaneous fractures • Bone & tooth malformation • Blue sclerae	Mutation in type I collagen
Scurvy	• Bleeding gums • Ecchymoses & petechiae • Impaired wound healing	Lack of vitamin C impairs collagen hydroxylation

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This patient likely has **vitamin C deficiency (scurvy)**. In the United States, vitamin C deficiency is seen primarily among malnourished populations, including alcoholics, the poor, and the elderly. The symptoms of scurvy reflect impaired formation of collagen and include gingival swelling/bleeding, petechiae, ecchymoses, and poor wound healing. Perifollicular hemorrhages and coiled (corkscrew) hairs are also commonly seen.

Collagen synthesis is a complex process that begins with the transcription of collagen genes in the nucleus **(Choice E)**. Collagen α-chains are then synthesized by rough endoplasmic reticulum (RER)-bound ribosomes and directed into the cisternae of the RER. Within the RER, specific **proline and lysine** residues are post-translationally **hydroxylated** to hydroxyproline and hydroxylysine by prolyl hydroxylase and lysyl

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(Choices A and B) After formation of the triple helix, procollagen molecules are secreted from the cell via the Golgi apparatus. Propeptides at the N- and C-terminals are cleaved by extracellular procollagen peptidase to form insoluble tropocollagen molecules. These monomers then self-assemble into collagen fibrils that are subsequently crosslinked via lysyl oxidase.

(Choices C and D) Lysosomes and mitochondria are not directly involved in the synthesis of collagen.

Educational objective:
The hydroxylation of proline and lysine residues in collagen helps it attain its maximum tensile strength. This process occurs in the rough endoplasmic reticulum and requires vitamin C as a cofactor. Impaired collagen synthesis resulting from vitamin C deficiency (scurvy) can lead to fragile vessels, predisposing to gingival bleeding, ecchymosis, and petechia.

References

- Be vigilant for scurvy in high-risk groups.

Biochemistry	Dermatology	Vitamin C deficiency
Subject	System	Topic

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This patient likely has **vitamin C deficiency (scurvy)**. In the United States, vitamin C deficiency is seen primarily among malnourished

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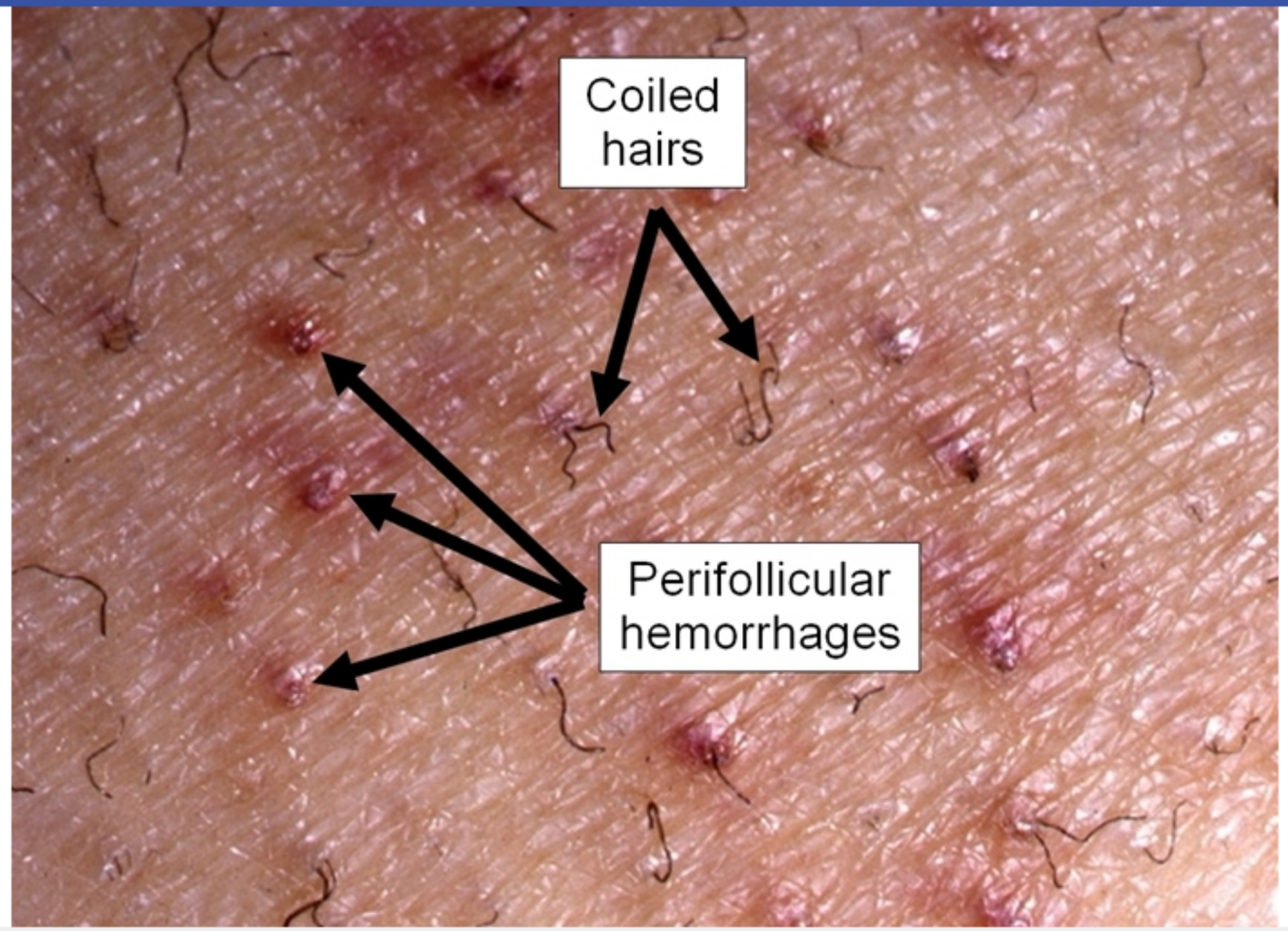

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This patient likely has **vitamin C deficiency (scurvy)**. In the United States, vitamin C deficiency is seen primarily among malnourished

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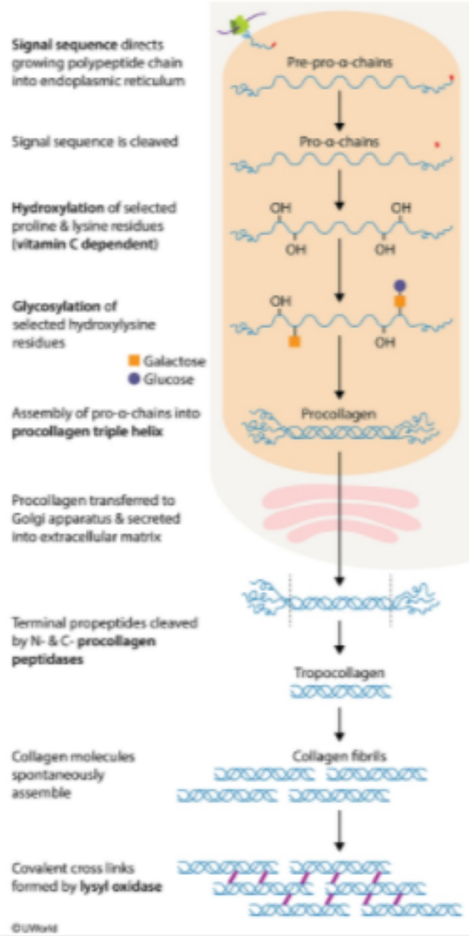
Collagen synthesis



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Hemoglobin C (HbC) disease is due to a single amino acid substitution (glutamic acid → lysine) at position 6 in the beta globin chain of the hemoglobin molecule. Hemoglobin S (HbS) is similar to HbC in that it is also formed by an amino acid substitution at position 6 in the beta globin chain. However, patients homozygous for HbC have mild chronic hemolytic anemia, whereas those homozygous for HbS generally have a more severe anemia complicated by vasoocclusive pain episodes. Which of the following properties best accounts for the differing clinical severity between the two conditions?

A. HbS allows hydrophobic interaction among hemoglobin molecules

B. HbS decreases beta globin interaction with 2,3-bisphosphoglycerate

C. HbS impairs oxygen unloading from the heme moiety

D. HbS prevents proper folding of the alpha helix in the beta globin chain

E. HbS stabilizes the iron moiety in the ferric (Fe^{3+}) state

Submit

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- ✓ A. HbS allows hydrophobic interaction among hemoglobin molecules (54%)
- B. HbS decreases beta globin interaction with 2,3-bisphosphoglycerate (6%)
- C. HbS impairs oxygen unloading from the heme moiety (8%)
- D. HbS prevents proper folding of the alpha helix in the beta globin chain (28%)
- E. HbS stabilizes the iron moiety in the ferric (Fe^{3+}) state (1%)

Omitted
Correct answer
A

54%
Answered correctly

02 secs
Time Spent

03/03/2020
Last Updated

Explanation

Globin chains in the hemoglobin tetramer are compactly folded due to nonpolar hydrophobic residues in the interior and charged polar residues on the surface. In **sickle cell disease**, the usual acidic (negatively charged) glutamic acid (glu) residue at the sixth position on the beta globin chain is replaced by a **nonpolar** (neutral charge) **valine** (val) residue, forming hemoglobin S (**HbS**). This single glu → val substitution leads to the formation of a **hydrophobic pocket** on the beta globin surface that interacts with a complementary nonpolar residue on another hemoglobin molecule. The hydrophobic interaction causes **polymerization** of HbS molecules and subsequent **erythrocyte sickling**, leading to membrane

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In patients with hemoglobin C (**HbC**), glu is replaced by a basic **polar** (positively charged) **lysine** (lys) residue. Because lys is charged (although it has opposite polarity to glu), there is no hydrophobic interaction between hemoglobin molecules and no polymerization/sickling. However, the positive charge of lys causes HbC to have decreased mobility on electrophoresis.

(Choice B) HbS and HbC do not differ significantly from normal hemoglobin in affinity to 2,3-bisphosphoglycerate (2,3-BPG). In addition, weaker interaction with 2,3-BPG would lead to increased oxygen affinity (left shift of the oxygen-hemoglobin dissociation curve), which would help ameliorate sickling.

(Choice C) The ability of HbS to polymerize helps stabilize the deoxygenated form, causing a right shift of the oxygen-hemoglobin dissociation curve that facilitates oxygen unloading. In contrast, impaired oxygen unloading occurs with carboxyhemoglobin due to an allosteric change that increases the affinity of the remaining 3 oxygen-binding sites.

(Choice D) A glu → val substitution affects the 3-dimensional (tertiary) structure of hemoglobin, but it does not result in a significant change in the alpha helical (secondary) structure. Introducing proline into the primary structure could distort the alpha helix due to proline's rigid cyclic structure.

(Choice E) HbS and HbC mutations do not involve amino acids lining the heme pocket. Heme iron oxidation (ferrous [Fe^{2+}] → ferric [Fe^{3+}]) results in methemoglobin formation. Hemoglobin M disease is a congenital cause of methemoglobinemia due to a mutation in the heme-binding pocket.

Educational objective:
Hemoglobin S (HbS) contains valine in place of glutamic acid at the sixth amino acid position of the beta globin chain. This promotes hydrophobic interaction among Hb molecules and results in HbS polymerization and erythrocyte sickling.

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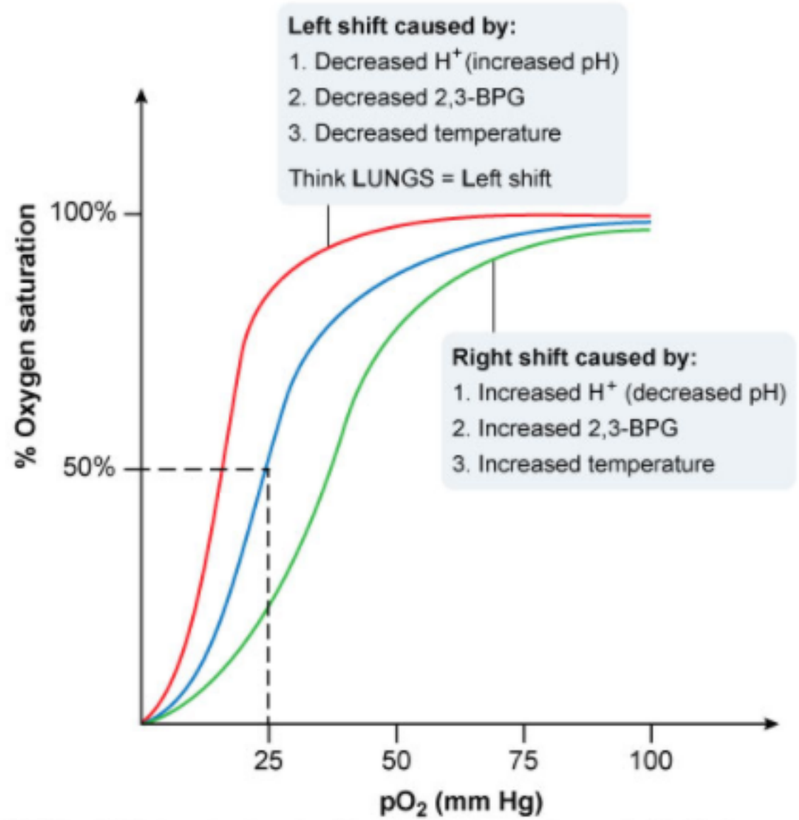
Exhibit Display

Oxygen-hemoglobin dissociation curve



2,3-BPG = 2,3-bisphosphoglycerate; pO_2 = partial pressure of oxygen in the blood.

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molecule. The hydrophobic interaction causes **polymerization** of HbS molecules and subsequent **erythrocyte sickling**, leading to membrane damage and permanent distortion of red blood cells. Red cell sickling is promoted by low oxygen levels, increased acidity, and dehydration.

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Educational objective:
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Biochemistry	Hematology & Oncology	Sickle cell
Subject	System	Topic

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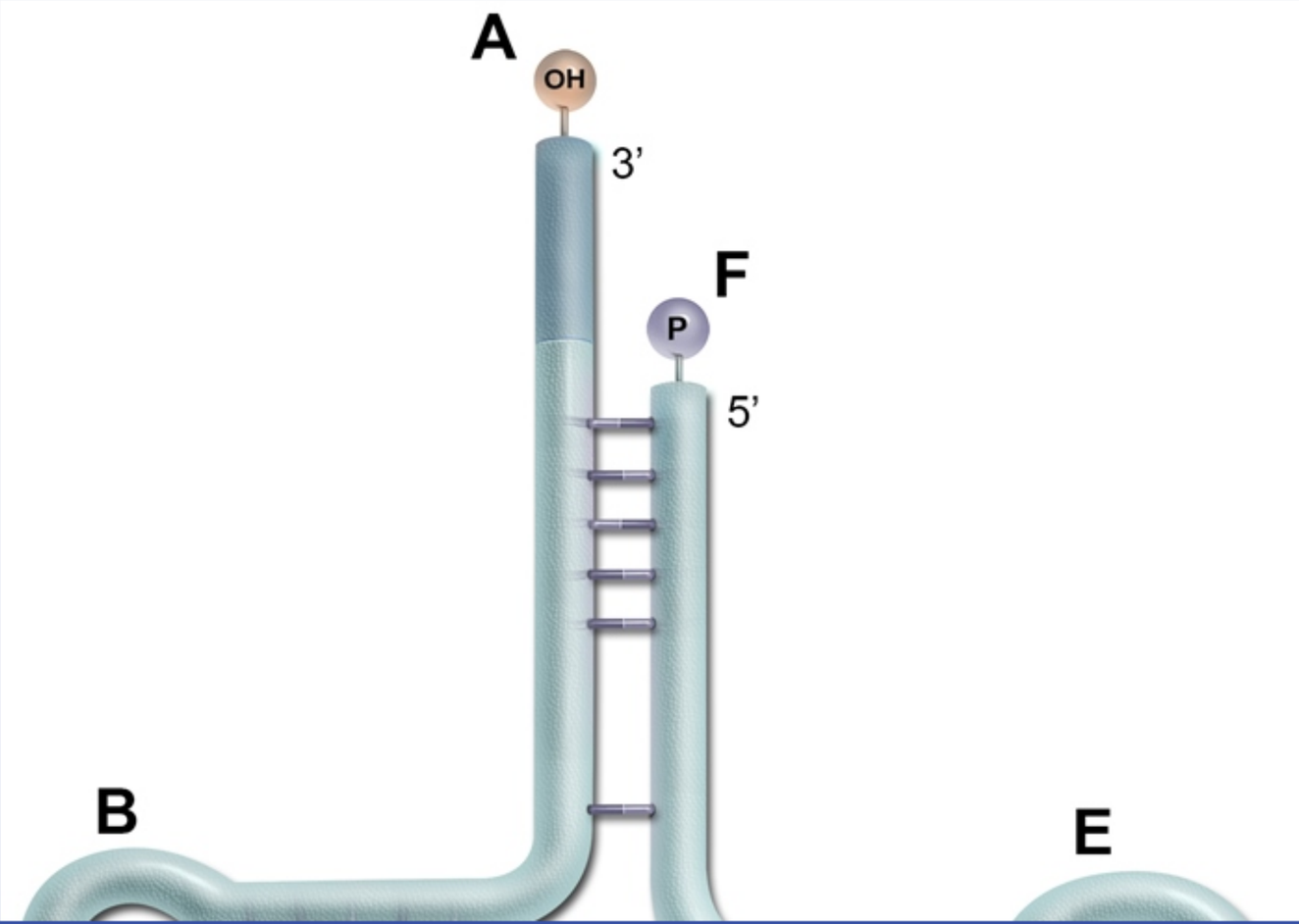
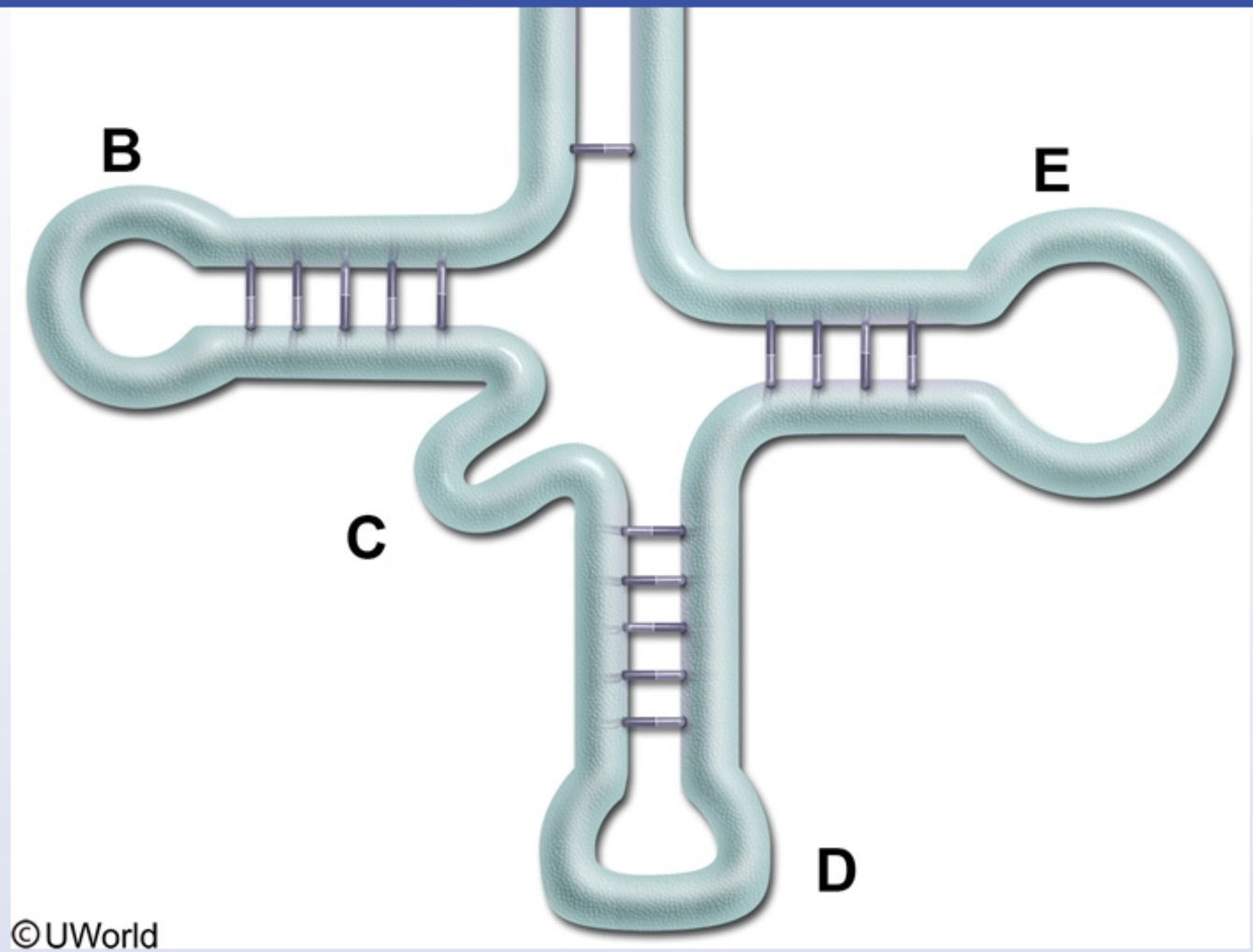
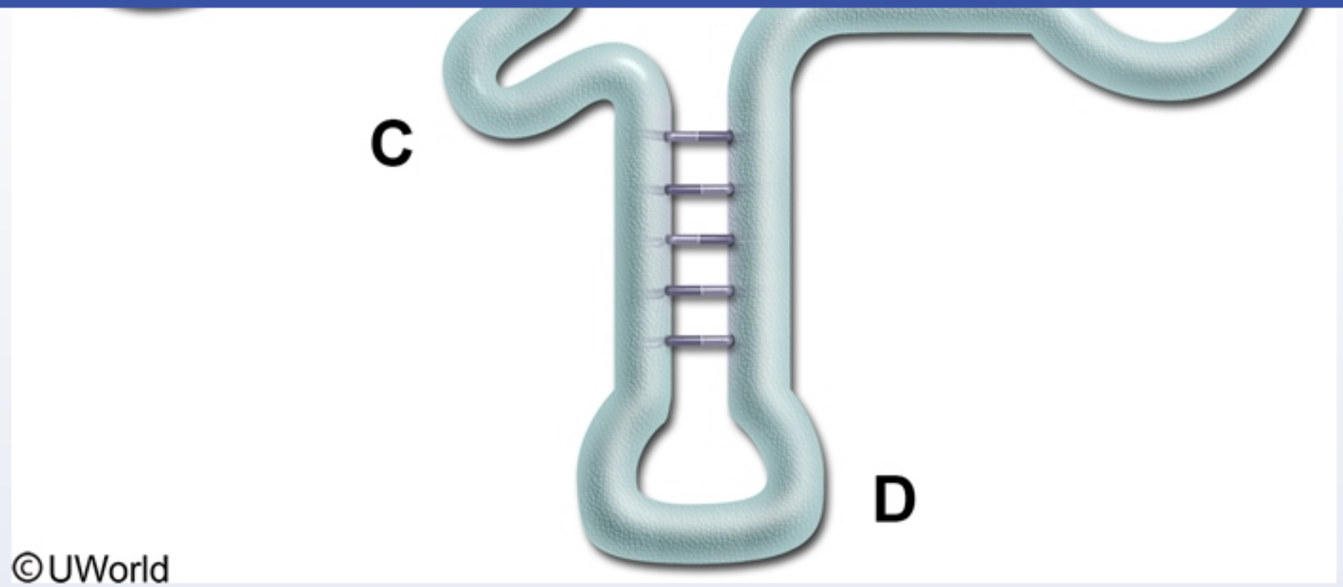
A geneticist is performing an experiment to alter protein structures by incorporating modified amino acids into their polypeptide sequences. During the process, she incubates dermal fibroblasts in a medium containing fluorescently labeled lysine residues. After several hours, she finds that aminoacyl tRNA synthetase in the fibroblasts "loads" lysine residues onto tRNA molecules containing the anticodon UUU. This residue most likely attaches to tRNA at which of the following sites in the image shown below?





A. A

B. B



A. A

B. B

C. C

D. D

E. E

F. F

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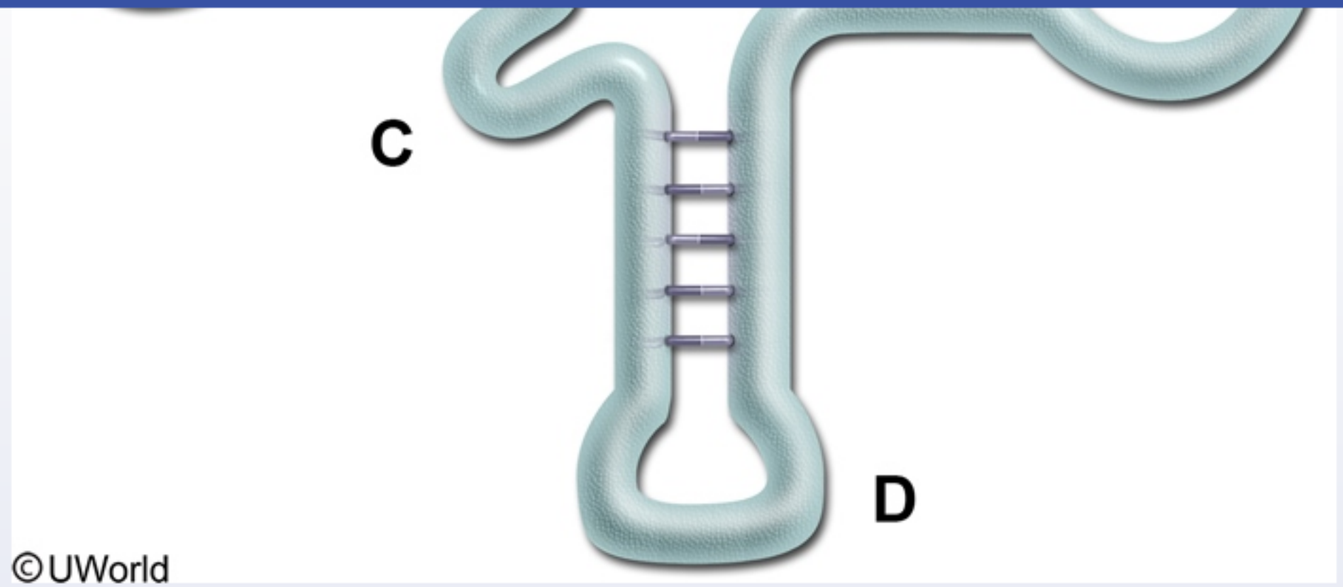

- ✓ A. A (67%)
- B. B (2%)
- C. C (2%)
- D. D (17%)
- E. E (2%)
- F. F (9%)

Omitted
Correct answer

67%
Answered correctly

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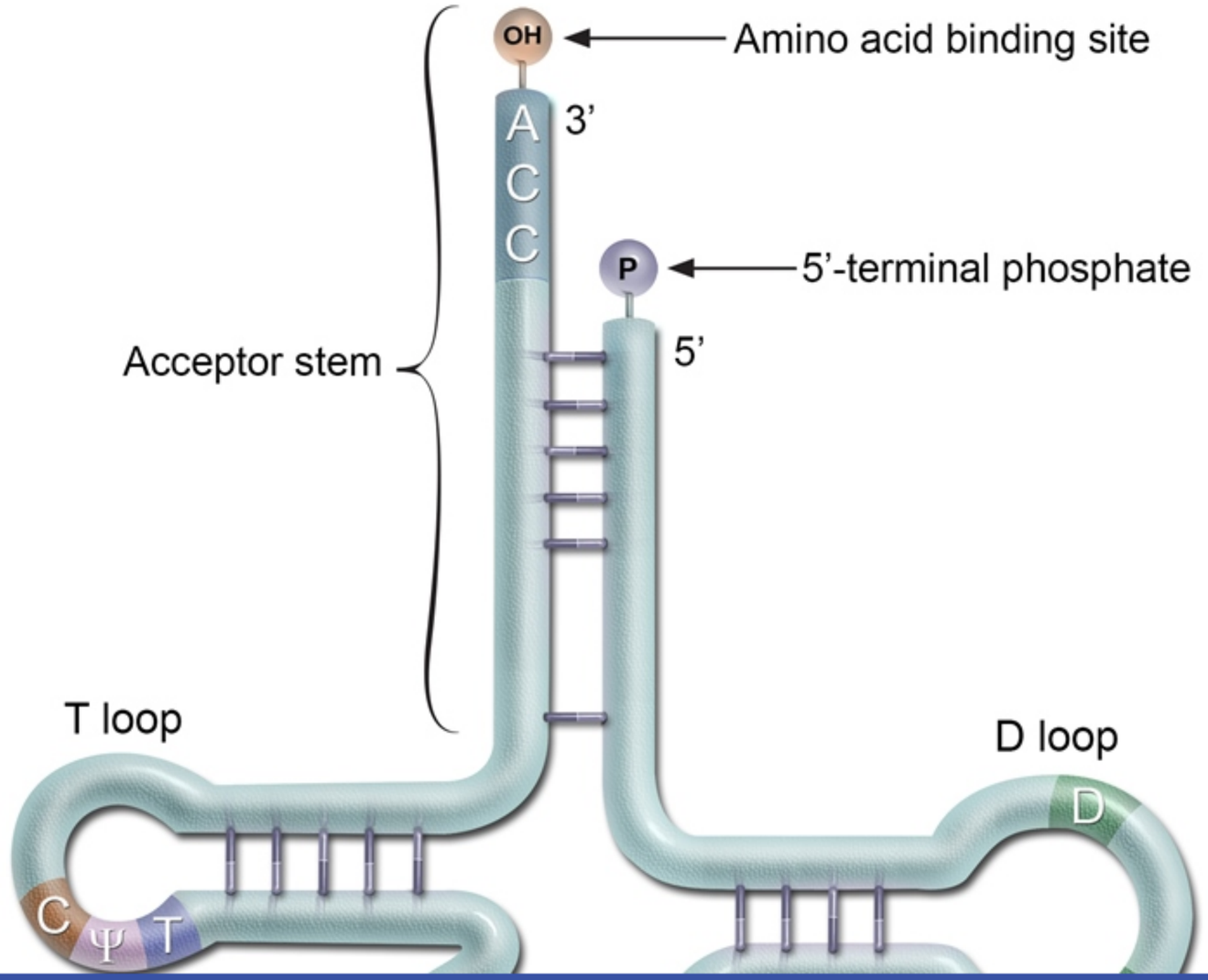
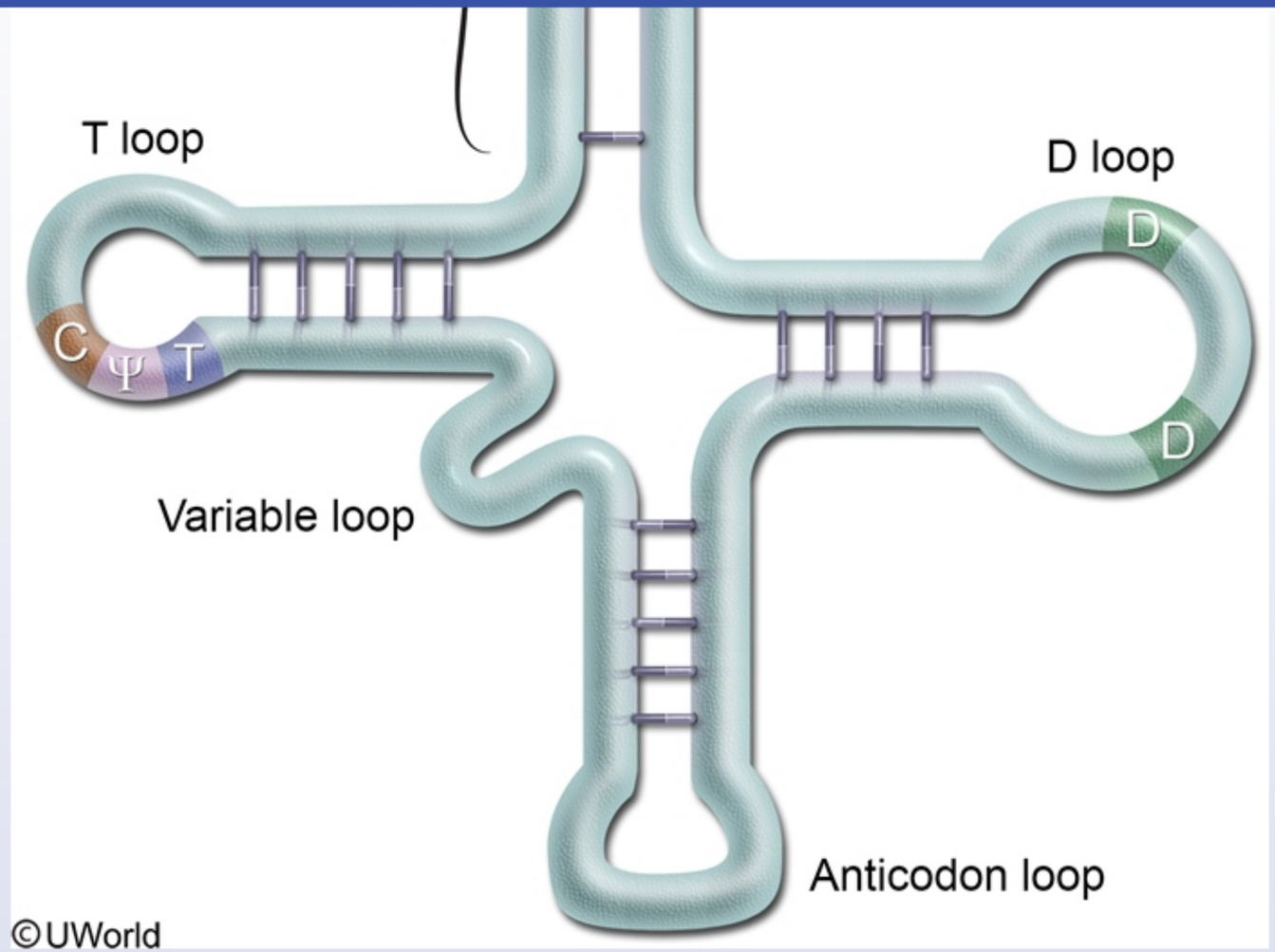
02/16/2020
Last Updated

Secondary structure of tRNA





The image above shows the "cloverleaf" secondary structure of **transfer RNA (tRNA)**, a small, noncoding subtype of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

The acceptor stem of tRNA is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. It contains the **CCA**

The image above shows the "cloverleaf" secondary structure of **transfer RNA (tRNA)**, a small, noncoding subtype of RNA that is responsible for transporting amino acids to the site of protein synthesis and introducing them into the growing polypeptide chain at the correct locations.

The acceptor stem of tRNA is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. It contains the **CCA tail**, which is added to the **3'** end of tRNA as a post-transcriptional modification and serves as the **amino acid binding site**. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice B) The T loop contains the TΨC sequence, which is necessary for the binding of tRNA to ribosomes. The TΨC sequence refers to the presence of the chemically modified bases ribothymidine and pseudouridine, and cytidine.

(Choice C) The variable loop contains a variable number of bases that lie between the T and anticodon loops. The variable loop is not present in all tRNAs.

(Choice D) The anticodon loop contains sequences that are complementary to the mRNA codon. During translation, the tRNA anticodon binds to the mRNA codon and assures placement of the proper amino acid in the growing polypeptide chain.

(Choice E) The D loop contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.

(Choice F) The 5' end of tRNA contains a terminal phosphate group that does not participate in amino acid or mRNA binding.

Educational objective:
The 3' CCA tail of tRNA serves as the amino acid binding site. Aminoacyl tRNA synthetase is the enzyme responsible for "loading" the appropriate amino acid to the 3' terminal hydroxyl group of the CCA tail.

References

- CCA addition to tRNA: implications for tRNA quality control.

Biochemistry	General Principles	Rna structure & function
Subject	System	Topic

A 39-year-old woman comes to the emergency department due to several episodes of severe upper abdominal pain. Her pain is triggered by fatty foods and resolves spontaneously. The symptoms first began a few months earlier after an uncomplicated pregnancy. Past medical history is notable for hypertension, for which the patient takes a calcium channel blocker, and hypertriglyceridemia, which is treated with a fibrate. Temperature is 37.2 C (98.9 F) and blood pressure is 143/76 mm Hg. The patient weighs 95 kg (210 lb) and is 173 cm (5 ft 8 in) tall. Ultrasound reveals thickening of the gallbladder wall, with tenderness elicited by the ultrasound probe directly over the gallbladder. She undergoes a laparoscopic cholecystectomy, with multiple stones noted in the contents of the gallbladder. Decreased activity of which of the following enzymes would most likely have contributed to this patient's condition?

A. Aromatase

B. β-glucuronidase

C. Cholesterol 7α-hydroxylase

D. HMG-CoA reductase

E. Thiolase

Submit

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- A. Aromatase (3%)
- B. β-glucuronidase (14%)
- ✓ C. Cholesterol 7α-hydroxylase (65%)
- D. HMG-CoA reductase (14%)
- E. Thiolase (2%)

Omitted
Correct answer
C

65%
Answered correctly

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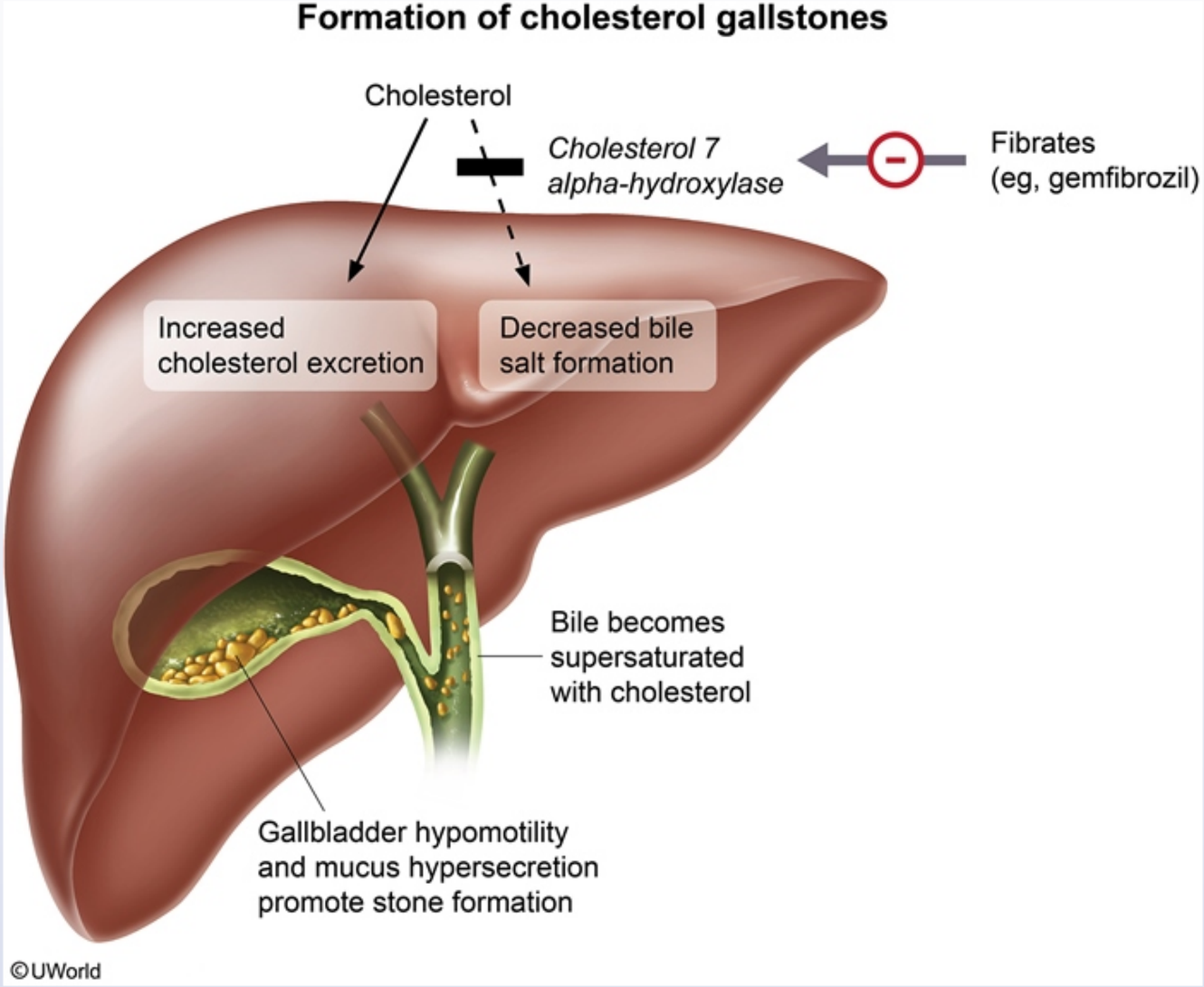
Last Updated

Explanation

Formation of cholesterol gallstones



This patient, with recurring abdominal pain, a positive "sonographic Murphy sign," and multiple cholesterol **gallstones**, has acute cholecystitis.

This patient, with recurring abdominal pain, a positive "sonographic Murphy sign," and multiple cholesterol **gallstones**, has acute cholecystitis. Water-insoluble **cholesterol** is secreted in bile, where it is solubilized by detergent-like bile salts and phosphatidylcholine. If there is more cholesterol than can be dissolved by the bile salts, it will precipitate into insoluble crystals, leading to formation of gallstones. Risk factors for gallstone formation include obesity or rapid weight loss, female sex, glucose intolerance, and hypomotility of the gallbladder (eg, pregnancy, prolonged fasting).

Fibrate medications (eg, fenofibrate, gemfibrozil) upregulate lipoprotein lipase, resulting in increased oxidation of fatty acids. In addition, fibrates inhibit **cholesterol 7α-hydroxylase**, which catalyzes the rate-limiting step in the synthesis of bile acids. The reduced bile acid production results in decreased cholesterol solubility in bile and favors the formation of cholesterol stones.

(Choice A) Estrogens increase the biosynthesis of cholesterol by upregulating hepatic HMG-CoA reductase activity. Estrogenic medications (eg, estrogen replacement therapy, combined oral contraceptives) increase the amount of cholesterol secreted in bile and contribute to formation of gallstones. Aromatase catalyzes the conversion of androgens to estrogen; inhibition would lead to reduced gallstone formation.

(Choice B) β-glucuronidase is released by damaged hepatocytes and bacteria in infected bile. It deconjugates bilirubin, and the resulting free bilirubin precipitates with calcium in the bile to form pigmented gallstones. Decreased activity of this enzyme would reduce the formation of pigmented stones but would not affect the formation of cholesterol gallstones.

(Choices D and E) The first step in cholesterol synthesis is the condensation of 2 molecules of acetyl-CoA by acetyl-CoA acetyl transferase (thiolase) to form acetoacetyl-CoA. Condensation with a third molecule of acetyl-CoA yields β-hydroxy-β-methylglutaryl-CoA (HMG-CoA). HMG-CoA reductase then catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol synthesis. Decreased activity of these enzymes would reduce cholesterol synthesis and the amount of cholesterol secreted in bile, discouraging cholesterol stone formation.

Educational objective:
Fibrate medications (eg, fenofibrate, gemfibrozil) inhibit cholesterol 7α-hydroxylase, which catalyzes the rate-limiting step in the synthesis of bile acids. The reduced bile acid production results in decreased cholesterol solubility in bile and favors the formation of cholesterol gallstones.

References

- Safety considerations with fibrate therapy.

prolonged fasting).

Fibrate medications (eg, fenofibrate, gemfibrozil) upregulate lipoprotein lipase, resulting in increased oxidation of fatty acids. In addition, fibrates inhibit **cholesterol 7α-hydroxylase**, which catalyzes the rate-limiting step in the synthesis of bile acids. The reduced bile acid production results in decreased cholesterol solubility in bile and favors the formation of cholesterol stones.

(Choice A) Estrogens increase the biosynthesis of cholesterol by upregulating hepatic HMG-CoA reductase activity. Estrogenic medications (eg, estrogen replacement therapy, combined oral contraceptives) increase the amount of cholesterol secreted in bile and contribute to formation of gallstones. Aromatase catalyzes the conversion of androgens to estrogen; inhibition would lead to reduced gallstone formation.

(Choice B) β-glucuronidase is released by damaged hepatocytes and bacteria in infected bile. It deconjugates bilirubin, and the resulting free bilirubin precipitates with calcium in the bile to form pigmented gallstones. Decreased activity of this enzyme would reduce the formation of pigmented stones but would not affect the formation of cholesterol gallstones.

(Choices D and E) The first step in cholesterol synthesis is the condensation of 2 molecules of acetyl-CoA by acetyl-CoA acetyl transferase (thiolase) to form acetoacetyl-CoA. Condensation with a third molecule of acetyl-CoA yields β-hydroxy-β-methylglutaryl-CoA (HMG-CoA). HMG-CoA reductase then catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol synthesis. Decreased activity of these enzymes would reduce cholesterol synthesis and the amount of cholesterol secreted in bile, discouraging cholesterol stone formation.

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References

- Safety considerations with fibrate therapy.

Biochemistry	Gastrointestinal & Nutrition	Gallstone disease
Subject	System	Topic

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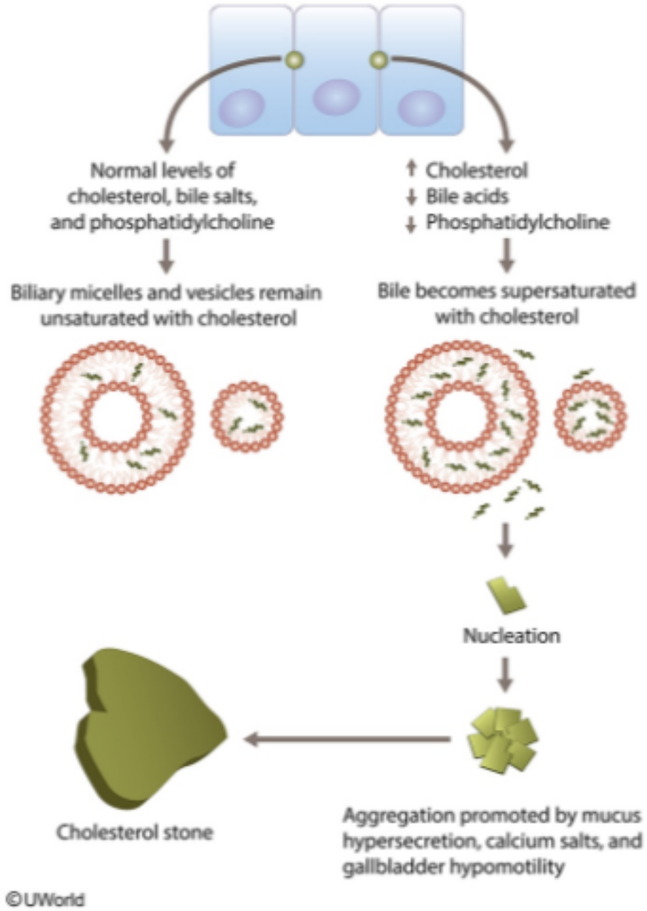
Pathogenesis of cholesterol gallstones



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Educational objective:

E. coli colonies grown on a lactose-containing medium up-regulate the production of the enzymes β-galactosidase and galactoside permease. Which of the following best explains the synchronous production of both enzymes in response to lactose?

- A. There are two activator binding sites for one activator protein
- B. There are two operators for one repressor protein
- C. There are two repressors for one inducer
- D. There are two promoters in close proximity to each other
- E. There is one mRNA coding for both enzymes

Submit

E. coli colonies grown on a lactose-containing medium up-regulate the production of the enzymes β-galactosidase and galactoside permease. Which of the following best explains the synchronous production of both enzymes in response to lactose?

A. There are two activator binding sites for one activator protein (11%)

B. There are two operators for one repressor protein (13%)

C. There are two repressors for one inducer (4%)

D. There are two promoters in close proximity to each other (14%)

✓ E. There is one mRNA coding for both enzymes (55%)

Omitted
Correct answer
E

55%
Answered correctly

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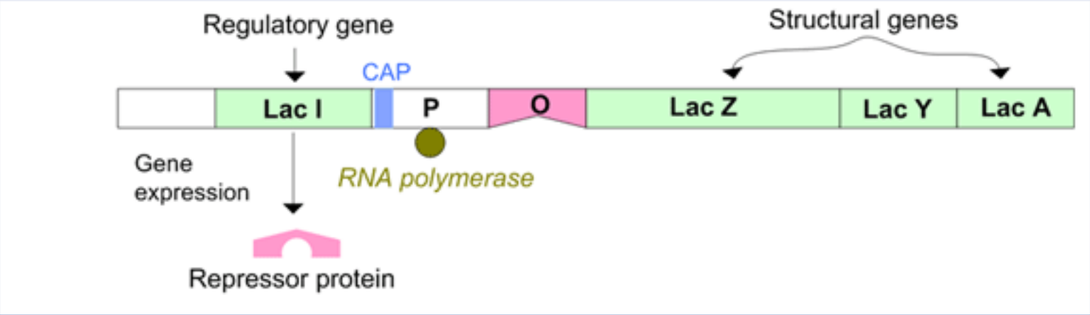
02/03/2020
Last Updated

Explanation



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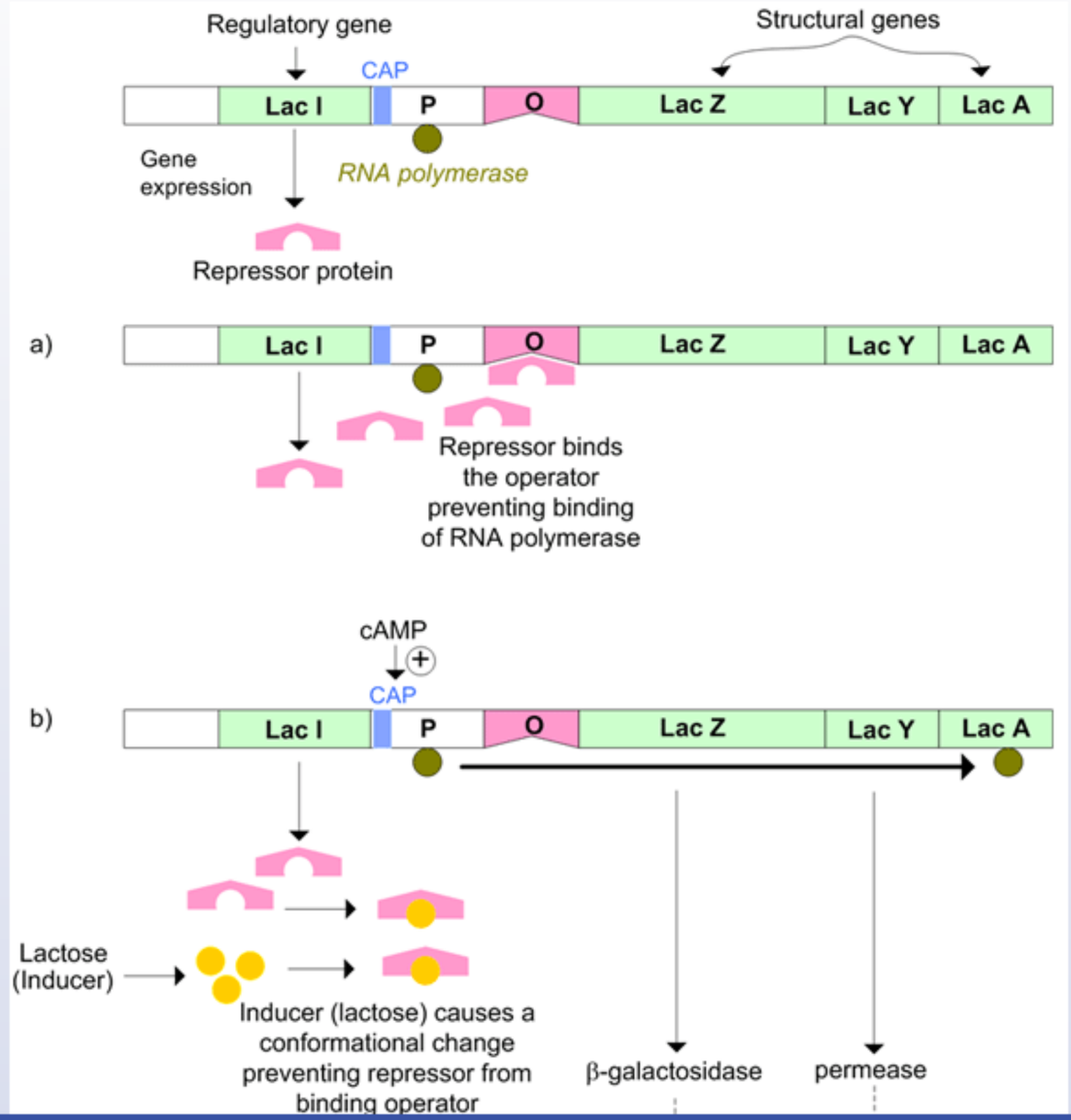

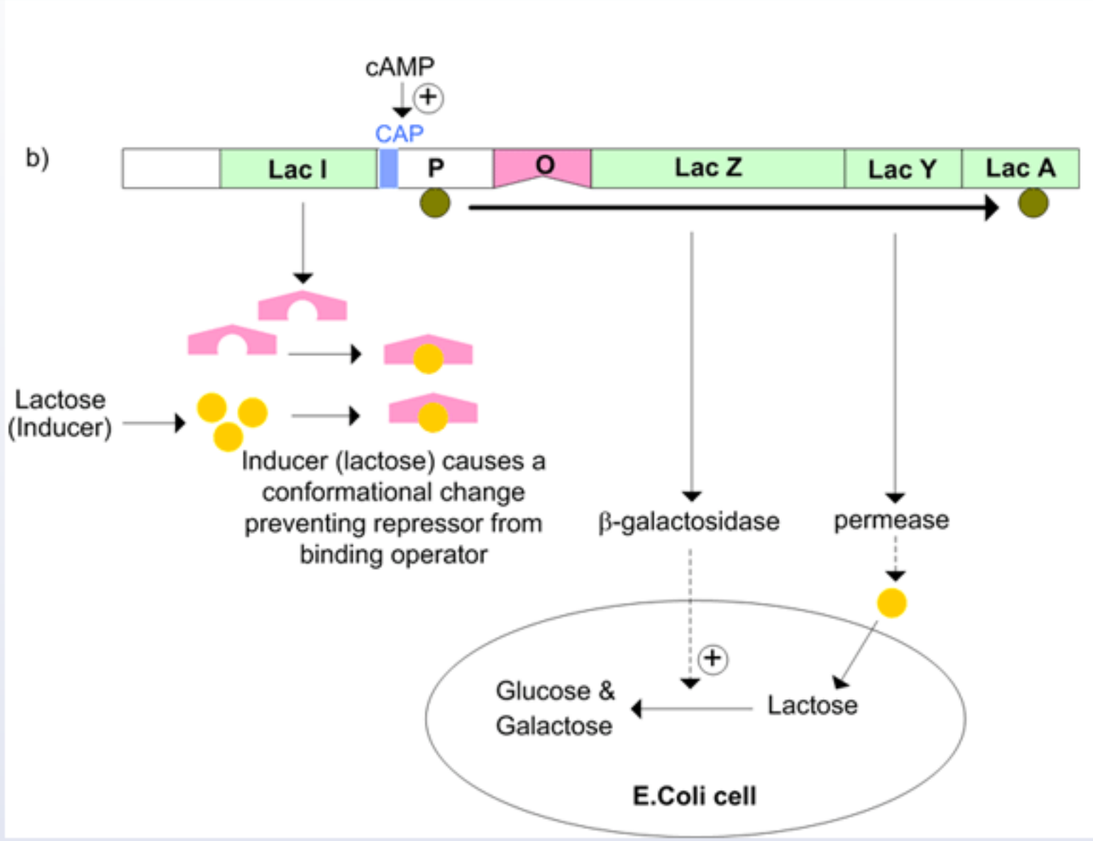

The *lac* operon is the sequence of the *E. coli* genome which is required for the metabolism of lactose. The *lac* operon consists of a regulatory gene (*i*), promoter region (*p*), operator region (*o*), and three structural genes (*z, y,* and *a*). The *z* gene codes for β-galactosidase (β-gal), which is primarily responsible for the hydrolysis of lactose to glucose and galactose. The *y* gene codes for permease, a transmembrane enzyme that increases the permeability of the cell to lactose. The *a* gene encodes a β-galactoside transacetylase, which transfers acetyl groups to β-galactosides and is unnecessary for lactose metabolism by *E. coli*.

In prokaryotes, one mRNA transcript contains the sequences for many proteins, and a single mRNA molecule can be translated into multiple proteins or polypeptides. For instance, all three proteins of the *lac* operon (β-galactosidase, permease, and transacetylase) are synthesized from

E.Coli cell

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In prokaryotes, one mRNA transcript contains the sequences for many proteins, and a single mRNA molecule can be translated into multiple proteins or polypeptides. For instance, all three proteins of the *lac* operon (β-galactosidase, permease, and transacetylase) are synthesized from a single mRNA molecule containing the *z, y,* and *a* gene sequences, respectively. Transcription and translation of the genes of the *lac* operon is typically synchronous. Remember that a single mRNA molecule which codes for more than one protein is referred to as a polycistronic mRNA, and while most prokaryotic mRNA molecules are polycistronic, eukaryotic mRNA is rarely polycistronic.

(Choices A – D) The lac operon, which codes for all three aforementioned proteins, is regulated by a single operator, a promoter, and a single group of regulatory elements: an inducer, repressor, and catabolite activator protein. Modulation of the transcription of this operon through binding of the operator and action of the repressor or other regulatory elements will change the transcription of all three *lac*-operon structural genes (*z, y,* and *a*). On the other hand, there are no operators, repressors, or inducers that can desynchronize the transcription of lac-operon structural genes.

Educational Objective:
Bacterial mRNA can be polycistronic, meaning that one mRNA codes for several proteins. An example of polycistronic mRNA is the bacterial lac operon, which codes for the proteins necessary for lactose metabolism by *E. coli*; the transcription and translation of these bacterial proteins is regulated by a single promoter, operator, and set of regulatory elements.

Biochemistry	Gastrointestinal & Nutrition	Lac operon
Subject	System	Topic

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A 54-year-old man comes to the emergency department with a 3-month history of fatigue and exertional dyspnea. He has early satiety and frequent upper abdominal discomfort. On physical examination, the patient has palpable splenomegaly but no lymphadenopathy. Laboratory tests are as follows:

Complete blood count	
Hemoglobin	9.2 mg/dL
Platelets	80,000/mm^3
Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

- A. Chromosomal position of the *BCR* and *ABL* genes
- B. DNA rearrangement in the *BCR* promoter region
- C. Fusion protein containing BCR and ABL domains
- D. Messenger RNA transcript containing *BCR* and *ABL* exons
- E. Point mutation in the *ABL* enhancer region

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Leukocytes	56,000/mm^3

Reverse transcription polymerase chain reaction is used to diagnose chronic myelogenous leukemia in this patient. Which of the following is most likely to be detected by this test?

A. Chromosomal position of the *BCR* and *ABL* genes (26%)

B. DNA rearrangement in the *BCR* promoter region (10%)

C. Fusion protein containing BCR and ABL domains (30%)

✓ D. Messenger RNA transcript containing *BCR* and *ABL* exons (28%)

E. Point mutation in the *ABL* enhancer region (3%)

Omitted
Correct answer
D

28%
Answered correctly

02 secs
Time Spent

02/29/2020
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Explanation

Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of **messenger RNA** (mRNA) in a sample. It is similar to regular PCR in that it uses sequence-specific primers, thermostable DNA polymerase, and a pool of deoxyribonucleoside triphosphates to amplify a DNA template. In RT-PCR, this template is generated by the action of **reverse transcriptase** on the mRNA sample, producing a complementary DNA (cDNA) strand that can then be amplified by PCR. Because cDNA is complementary to the mRNA sequence, it contains the **exons** of a gene along with the 5′ and 3′ untranslated regions.

Chronic myelogenous leukemia (CML) is characterized by uncontrolled proliferation of the myeloid stem cell line due to a chromosomal translocation. This translocation causes the *BCR* gene on chromosome 22 to fuse with the *ABL* gene on chromosome 9, forming the *BCR-ABL* fusion gene. The BCR-ABL fusion protein product is a constitutively active tyrosine kinase that accelerates cell division and increases genetic instability. RT-PCR can be used to identify mRNA transcribed from the *BCR-ABL* fusion gene and therefore diagnose CML.

(Choice A) Fluorescence in situ hybridization (FISH) techniques allow direct localization of genes to their respective chromosomes by using a labeled DNA probe complementary to the sequence of interest.

(Choices B and E) RT-PCR amplification uses an mRNA template, so it cannot detect changes in the parts of the gene that are not transcribed (eg, promoter and enhancer regions). Other PCR techniques that use chromosomal DNA can detect changes in these nontranscribed regions.

(Choice C) RT-PCR is used to detect levels of mRNA expression; it does not identify proteins. A Western blot study can detect the BCR-ABL protein by using monoclonal antibodies directed against BCR or ABL.

Educational objective:
Reverse transcription polymerase chain reaction (RT-PCR) is used to detect and quantify levels of mRNA in a sample. It uses reverse transcription to create a complementary DNA template that is then amplified using the standard PCR procedure. RT-PCR can be used to diagnose chronic myelogenous leukemia by identifying an mRNA transcript containing both *BCR* and *ABL* exons in affected cells.

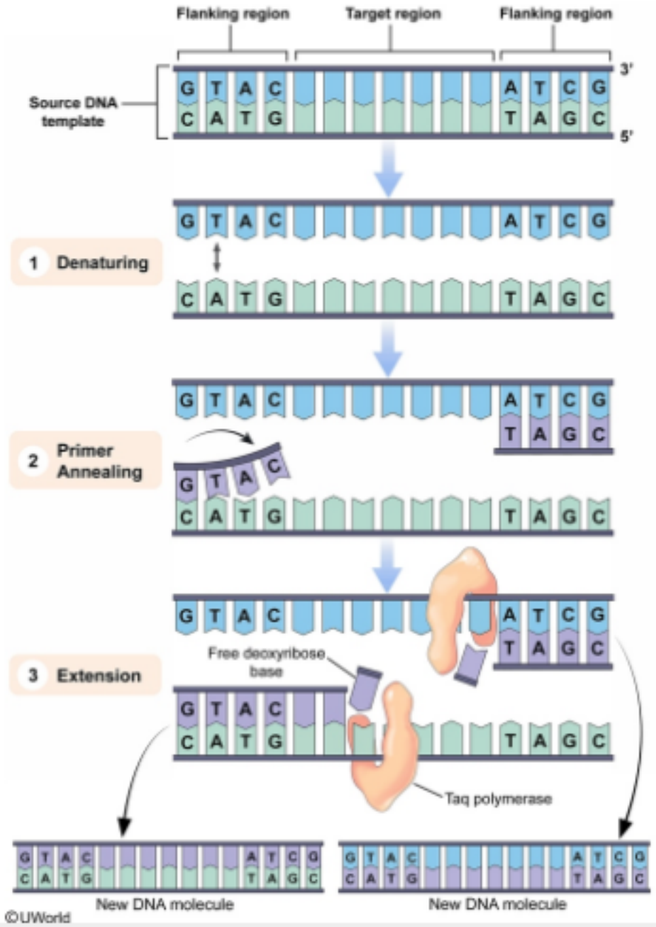
References

- Real time polymerase chain reaction in diagnosis of chronic myeloid leukemia.

Explanation

Exhibit Display

Polymerase chain reaction



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References

- Real time polymerase chain reaction in diagnosis of chronic myeloid leukemia.

Biochemistry	General Principles	Polymerase chain reaction
Subject	System	Topic

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A research scientist is studying biochemical reactions that take place in the liver. He cultures hepatocytes in a growth media enriched with glutamate labeled with nitrogen isotopes. After some time, he finds that the nitrogen isotopes are transferred to oxaloacetate, forming aspartate in the process. Which of the following substances is most likely involved in this reaction?

- A. Biotin
- B. Folic acid
- C. Niacin
- D. Pyridoxine
- E. Riboflavin
- F. Thiamine

Submit

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A. Biotin (19%)
B. Folic acid (2%)
C. Niacin (11%)
✓ D. Pyridoxine (48%)
E. Riboflavin (6%)
F. Thiamine (12%)

Omitted
Correct answer
D

48%
Answered correctly

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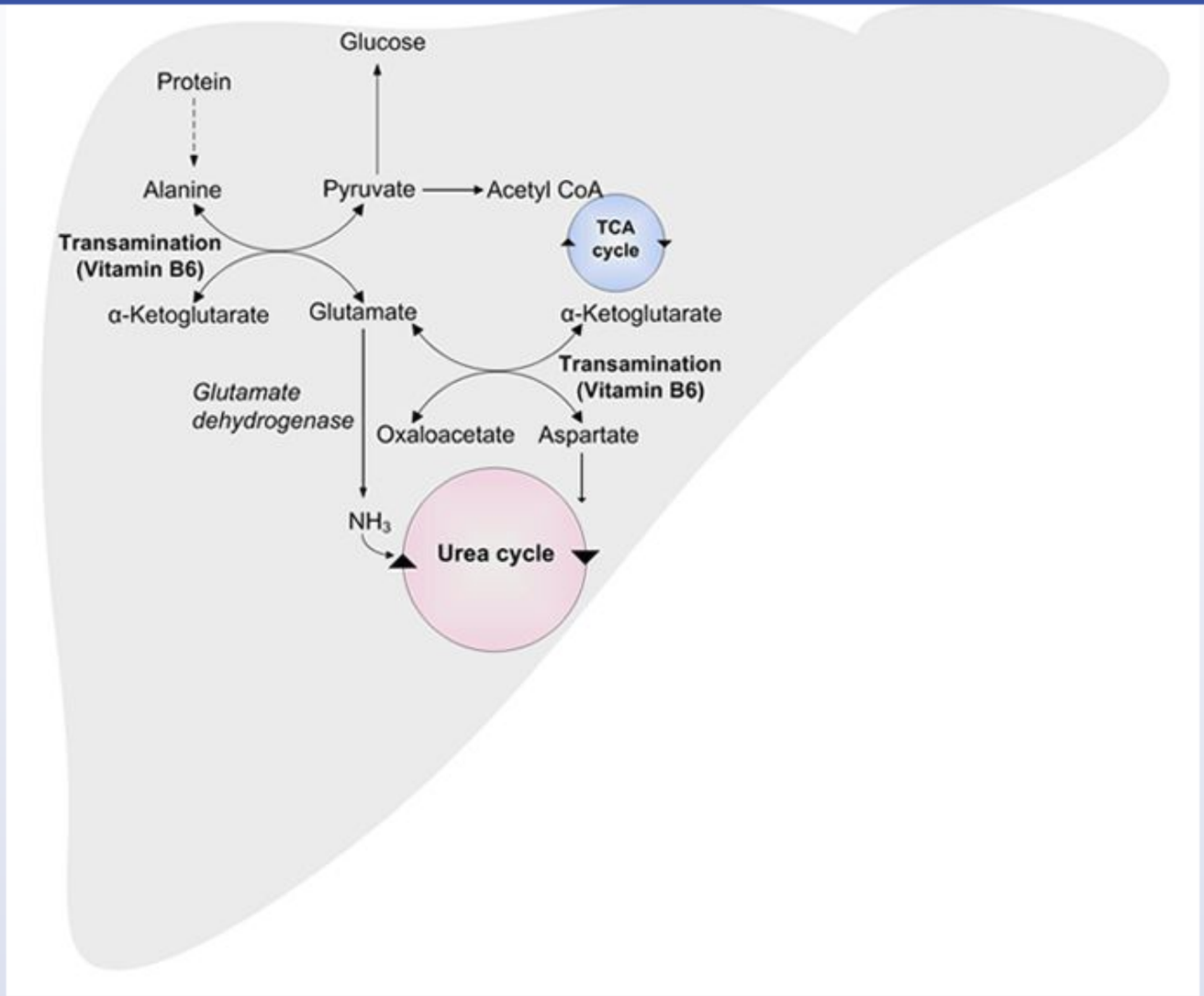
Explanation



Pyridoxine (vitamin B_6) is necessary for the transamination and decarboxylation of amino acids, for gluconeogenesis, and for other essential biochemical processes. **Transamination reactions** typically occur between an **amino acid** and an **α-keto acid**. The amino group is transferred

Pyridoxine (vitamin B_6) is necessary for the transamination and decarboxylation of amino acids, for gluconeogenesis, and for other essential biochemical processes. **Transamination reactions** typically occur between an **amino acid** and an **α-keto acid**. The amino group is transferred to the α-keto acid from the amino acid, and the α-keto acid thereby becomes an amino acid. For example, glutamate (amino acid) reacts with oxaloacetate (α-keto acid) to form aspartate (the resulting amino acid) and α-ketoglutarate (the resulting α-keto acid).

Transaminases (aminotransferases) are the enzymes that catalyze transamination reactions, and pyridoxal phosphate (active vitamin B_6) serves as an essential cofactor for the transaminase.

(Choice A) Biotin (vitamin B_7) is a cofactor for all 4 carboxylase enzymes: pyruvate carboxylase, acetyl-CoA carboxylase, propionyl-CoA carboxylase, and 3-methylcrotonyl-CoA-carboxylase.

(Choice B) Folic acid (vitamin B_9) is an essential cofactor in nucleic acid synthesis, and a deficiency of either folate or vitamin B_{12} results in megaloblastic anemia.

(Choice C) Many dehydrogenases use NAD+ and NADP+, which are formed from niacin. Niacin (vitamin B_3, or nicotinic acid) deficiency is known as pellagra and is classically associated with the 4 Ds: dermatitis, dementia, diarrhea, and, if untreated, death.

(Choice E) Riboflavin (vitamin B_2) is used in dehydrogenase reactions involving FMN and FAD.

(Choice F) Thiamine (vitamin B_1) serves as a coenzyme for a number of important dehydrogenase enzymes, including transketolase, α-ketoglutarate dehydrogenase, and pyruvate dehydrogenase.

Educational objective:
Transamination reactions typically occur between an amino acid and an α-keto acid. The amino group from the amino acid is transferred to the α-keto acid, and the α-keto acid in turn becomes an amino acid. Pyridoxal phosphate (active vitamin B_6) serves as a cofactor in amino acid transamination and decarboxylation reactions.

References

- Review: the role of coenzymes in clinical enzymology.
- An appreciation of Professor Alexander E. Braunstein. The discovery and scope of enzymatic transamination.

A pharmaceutical researcher develops a novel antibacterial drug that works by inhibiting exonuclease activity during DNA replication. When actively dividing *Escherichia coli* is exposed to the drug, enzyme-mediated nucleotide removal in the 5' to 3' direction is impaired, leading to inhibition of bacterial growth. Which of the following enzymes is the most likely target of this drug?

- A. DNA polymerase I
- B. DNA polymerase III
- C. Gyrase
- D. Helicase
- E. Ligase
- F. Primase

Submit

A pharmaceutical researcher develops a novel antibacterial drug that works by inhibiting exonuclease activity during DNA replication. When actively dividing *Escherichia coli* is exposed to the drug, enzyme-mediated nucleotide removal in the 5' to 3' direction is impaired, leading to inhibition of bacterial growth. Which of the following enzymes is the most likely target of this drug?

- ✓ A. DNA polymerase I (58%)
- B. DNA polymerase III (28%)
- C. Gyrase (3%)
- D. Helicase (2%)
- E. Ligase (3%)
- F. Primase (3%)

Omitted
Correct answer
A

58%
Answered correctly

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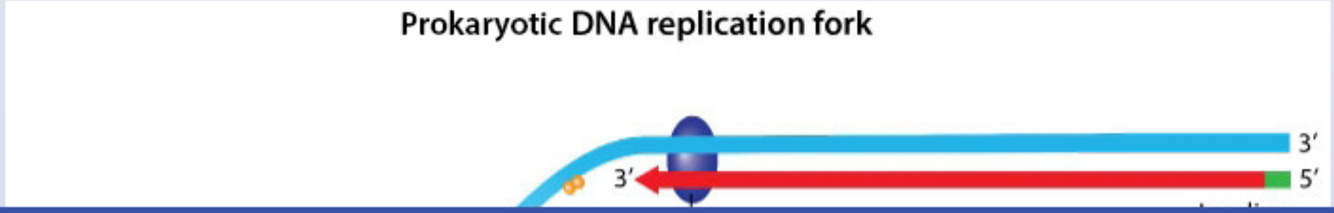
Explanation



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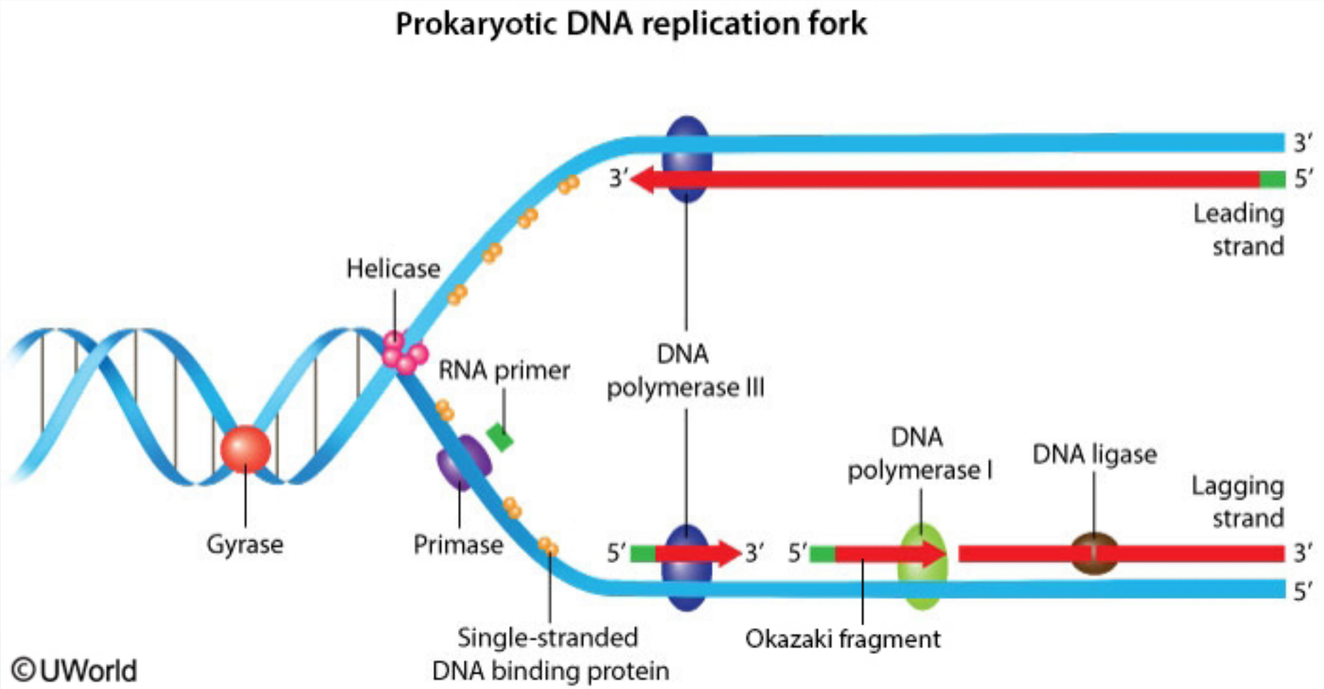

DNA polymerases are the primary enzymes responsible for DNA synthesis, which occurs in the 5' to 3' direction. **Prokaryotes** such as *Escherichia coli* have 3 major DNA polymerases: I, II, and III. DNA replication requires a high degree of fidelity to preserve the genetic code in daughter cells and prevent potentially lethal mutations. This high-fidelity replication is accomplished by the 3' to 5' "proofreading" exonuclease activity of all 3 DNA polymerases.

DNA polymerase I is unique as it is the only prokaryotic polymerase that also has **5' to 3' exonuclease activity**. This activity functions to **remove the RNA primer** created by RNA primase and **repair damaged DNA** sequences.

(Choice B) DNA polymerase III has 5' to 3' polymerase and 3' to 5' exonuclease activity; however, it does not possess 5' to 3' exonuclease activity.

activity of all 3 DNA polymerases.

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(Choice B) DNA polymerase III has 5' to 3' polymerase and 3' to 5' exonuclease activity; however, it does not possess 5' to 3' exonuclease activity.

(Choice C) The enzyme topoisomerase II, also known as DNA gyrase in prokaryotes, relieves tension created during DNA strand unwinding by introducing negative supercoils into the circular DNA. Fluoroquinolones (eg, ciprofloxacin) are a class of antibiotics that work by inhibiting DNA gyrase.

(Choice D) Before DNA replication begins, helicase unwinds the DNA double helix, facilitating separation of the 2 DNA strands by single-stranded DNA-binding proteins.

(Choice E) Okazaki fragments of the lagging strand are bound together by the enzyme ligase.

(Choice F) DNA polymerases cannot begin synthesizing complementary DNA on a single-stranded template without an RNA primer. Primase is an RNA polymerase that synthesizes this primer, which is made up of short stretches of RNA base paired to the DNA template.

Educational objective:
In prokaryotes, DNA polymerase I has 5' to 3' exonuclease activity in addition to 5' to 3' polymerase and 3' to 5' exonuclease activities. This 5' to 3' exonuclease activity functions to remove the RNA primer created by RNA primase and repair damaged DNA sequences.

References

- DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.

Biochemistry	General Principles	Dna replication
Subject	System	Topic

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A 32-year-old man is recovering from extensive burns. Fibroblasts near the site of injury actively synthesize precursor mRNA to be used as templates for protein synthesis. After transcription, extensive processing of the precursor RNA occurs to form the finalized mRNA sequence. The finalized mRNA then exits the nucleus and undergoes translation by ribosome complexes before being degraded. Which of the following steps involving the processing and handling of mRNA occurs only within the cytoplasm of cells?

- A. 5'-terminal guanosine triphosphate addition
- B. Methylation of the 5'-terminal guanine
- C. Multiple adenine nucleotide attachment to the 3'-end
- D. Interaction with snRNP
- E. Removal of intervening sequences
- F. Interaction with P bodies

Submit

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- A. 5'-terminal guanosine triphosphate addition (6%)
- B. Methylation of the 5'-terminal guanine (13%)
- C. Multiple adenine nucleotide attachment to the 3'-end (11%)
- D. Interaction with snRNP (14%)
- E. Removal of intervening sequences (8%)
- ✓ F. Interaction with P bodies (44%)

Omitted
Correct answer
F

44%
Answered correctly

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Explanation

After transcription, the preliminary, unprocessed mRNA is known as precursor mRNA, or heterogeneous nuclear RNA (hnRNA). Eukaryotic pre-mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

Once mRNA is finalized, it leaves the nucleus bound to specific packaging proteins. Upon entering the cytoplasm, these mRNA complexes often

After transcription, the preliminary, unprocessed mRNA is known as precursor mRNA, or heterogeneous nuclear RNA (hnRNA). Eukaryotic pre-mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

Once mRNA is finalized, it leaves the nucleus bound to specific packaging proteins. Upon entering the cytoplasm, these mRNA complexes often associate with ribosomes to undergo translation. However, certain mRNA sequences instead associate with proteins that are found in P bodies. P bodies are distinct foci found within eukaryotic cells that are involved in mRNA regulation and turnover. They play a fundamental role in translation repression and mRNA decay, and contain numerous proteins including RNA exonucleases, mRNA decapping enzymes, and constituents involved in mRNA quality control and microRNA-induced mRNA silencing. P bodies also seem to function as a form of mRNA storage, as certain mRNAs are incorporated into P bodies only to be later released and utilized for protein translation.

(Choices A and B) The 5' end of all mRNA is capped with a 7-methylguanosine residue by a unique 5' to 5' linkage, which occurs in two stages. The first step is the addition of guanine triphosphate to the 5' end of mRNA in a reaction catalyzed by guanylyltransferase. Methylation of the guanosine cap is then catalyzed by guanine-7-methyltransferase. Capping of the precursor RNA occurs in the nucleus as the RNA is being transcribed. This methylated cap protects mRNA from degradation by cellular exonucleases, and allows it to exit the nucleus.

(Choice C) mRNA is polyadenylated at the 3' end by the polyadenylate polymerase complex, which recognizes a specific sequence (AAUAAA), cleaves the pre-mRNA molecule a few residues downstream from this sequence, and then adds a stretch of 20 - 250 adenine residues called the poly A tail. The addition of the poly A tail occurs before the mRNA exits the nucleus. In the cytosol, the poly A tail is gradually shortened, eventually leading to mRNA degradation.

(Choices D and E) Since pre-mRNA contains both introns and exons, and only exons code for proteins, introns must be excised before translation through a process known as splicing. Splicing of pre-mRNA occurs within the nucleus and is facilitated by the interaction of pre-mRNA with small ribonucleoprotein particles called snRNPs (or "snurps" for short).

Educational objective:
When mRNA is first transcribed from DNA, it is in an unprocessed form called pre-mRNA or heterogeneous nuclear mRNA (hnRNA). Several processing steps are required before finalized mRNA molecules can leave the nucleus, including 5'-capping, poly A tail addition, and intron splicing. Cytoplasmic P bodies play an important role in mRNA translation regulation and mRNA degradation.

Once mRNA is finalized, it leaves the nucleus bound to specific packaging proteins. Upon entering the cytoplasm, these mRNA complexes often associate with ribosomes to undergo translation. However, certain mRNA sequences instead associate with proteins that are found in P bodies. P bodies are distinct foci found within eukaryotic cells that are involved in mRNA regulation and turnover. They play a fundamental role in translation repression and mRNA decay, and contain numerous proteins including RNA exonucleases, mRNA decapping enzymes, and constituents involved in mRNA quality control and microRNA-induced mRNA silencing. P bodies also seem to function as a form of mRNA storage, as certain mRNAs are incorporated into P bodies only to be later released and utilized for protein translation.

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(Choices D and E) Since pre-mRNA contains both introns and exons, and only exons code for proteins, introns must be excised before translation through a process known as splicing. Splicing of pre-mRNA occurs within the nucleus and is facilitated by the interaction of pre-mRNA with small ribonucleoprotein particles called snRNPs (or "snurps" for short).

Educational objective:
When mRNA is first transcribed from DNA, it is in an unprocessed form called pre-mRNA or heterogeneous nuclear mRNA (hnRNA). Several processing steps are required before finalized mRNA molecules can leave the nucleus, including 5'-capping, poly A tail addition, and intron splicing. Cytoplasmic P bodies play an important role in mRNA translation regulation and mRNA degradation.

References

- Regulation of mRNA cap methylation.

A dermatology researcher is studying the role of different amino acids in wound healing. She cultures mature dermal fibroblasts in growth media. After several days, the fibroblasts begin synthesizing polypeptide chains that assemble into triple helical structures, followed by fibrils. The fibrillar proteins are hydrolyzed and separated into their constituent amino acids via paper chromatography. Which of the following amino acids is most likely to be found in highest quantity in these proteins?

- A. Alanine
- B. Cysteine
- C. Glycine
- D. Leucine
- E. Lysine
- F. Proline

Submit

A dermatology researcher is studying the role of different amino acids in wound healing. She cultures mature dermal fibroblasts in growth media. After several days, the fibroblasts begin synthesizing polypeptide chains that assemble into triple helical structures, followed by fibrils. The fibrillar proteins are hydrolyzed and separated into their constituent amino acids via paper chromatography. Which of the following amino acids is most likely to be found in highest quantity in these proteins?

- A. Alanine (1%)
- B. Cysteine (3%)
- ✓ C. Glycine (56%)
- D. Leucine (2%)
- E. Lysine (12%)
- F. Proline (24%)

Omitted
Correct answer
C

56%
Answered correctly

02 secs
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Explanation

Collagen is the most abundant protein in the human body and is synthesized by fibroblasts, osteoblasts, and chondroblasts. It consists of 3 polypeptide **alpha chains** held together by hydrogen bonds, forming a rope-like **triple helix** (collagen molecule). Collagen molecules self-assemble into fibrils, which subsequently crosslink to form collagen fibers.

The triple helical conformation of collagen molecules occurs due to the simple and repetitive amino acid sequence within each alpha chain, in

C

Explanation

Collagen is the most abundant protein in the human body and is synthesized by fibroblasts, osteoblasts, and chondroblasts. It consists of 3 polypeptide **alpha chains** held together by hydrogen bonds, forming a rope-like **triple helix** (collagen molecule). Collagen molecules self-assemble into fibrils, which subsequently crosslink to form collagen fibers.

The triple helical conformation of collagen molecules occurs due to the simple and repetitive amino acid sequence within each alpha chain, in which **glycine** (Gly) occupies **every third amino acid** position (Gly-X-Y). Glycine is the most abundant amino acid in collagen and, due to its small size, is the only amino acid that can fit into the confined space between individual alpha chains.

(Choices A, B, D, E, and F) None of the other amino acids are as abundant as glycine in collagen. X often represents proline and Y is often hydroxyproline or hydroxylysine. Proline residues are essential for alpha helix formation because their ring configuration introduces a kink in the polypeptide chain, enhancing the rigidity of the helical structure. Hydroxylysine is necessary for cross-linking, which greatly increases the tensile strength of assembled collagen fibers.

Educational objective:
Glycine is the most abundant amino acid in collagen. The triple helical conformation of collagen molecules occurs due to the repetitive amino acid sequence within each alpha chain, in which glycine (Gly) occupies every third amino acid position (Gly-X-Y).

References

- Collagen structure and stability.

Biochemistry	General Principles	Protein structure
Subject	System	Topic

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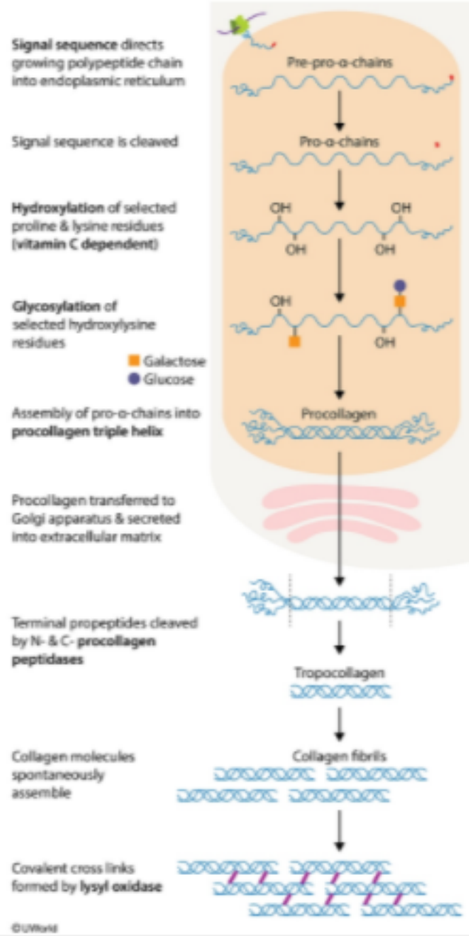
C

Exhibit Display

Collagen synthesis



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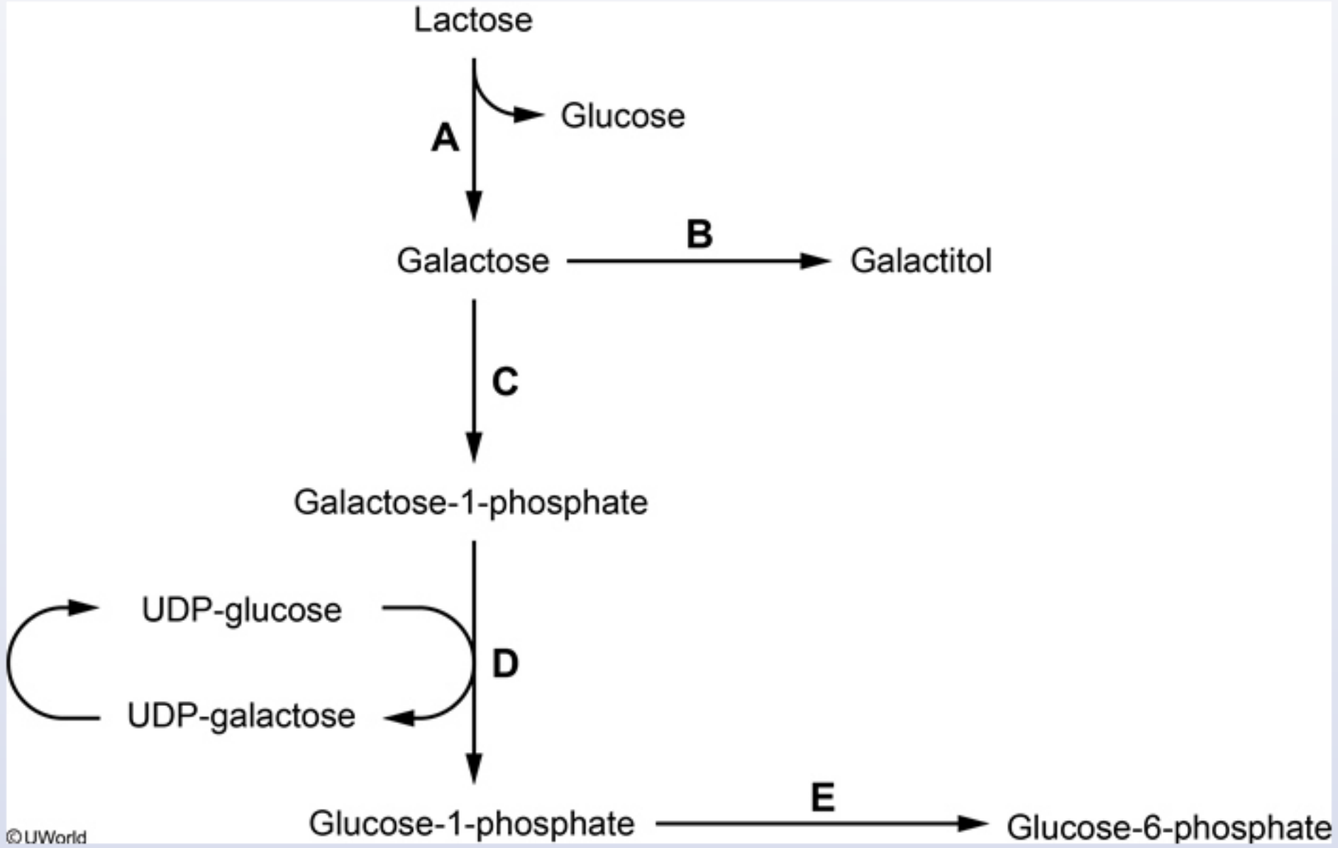
A 5-day-old term newborn is brought to the emergency department for multiple episodes of emesis. The breastfed infant has been having fewer wet diapers over the last 2 days. Vital signs show tachycardia, tachypnea, and hypotension. Physical examination shows an icteric, lethargic baby with a sunken fontanelle, dry mucous membranes, and hepatomegaly. A blood culture is drawn and empiric antibiotics are initiated. Hematologic studies show leukocytosis with bandemia. Serum studies show hypoglycemia and elevated transaminases. The ammonia level is normal. Newborn screen is pending. Preliminary results from arterial blood culture show gram-negative rods. The infant is placed on a special formula and gradually improves over the next few days. Which of the following steps in metabolism is most likely impaired in this patient?



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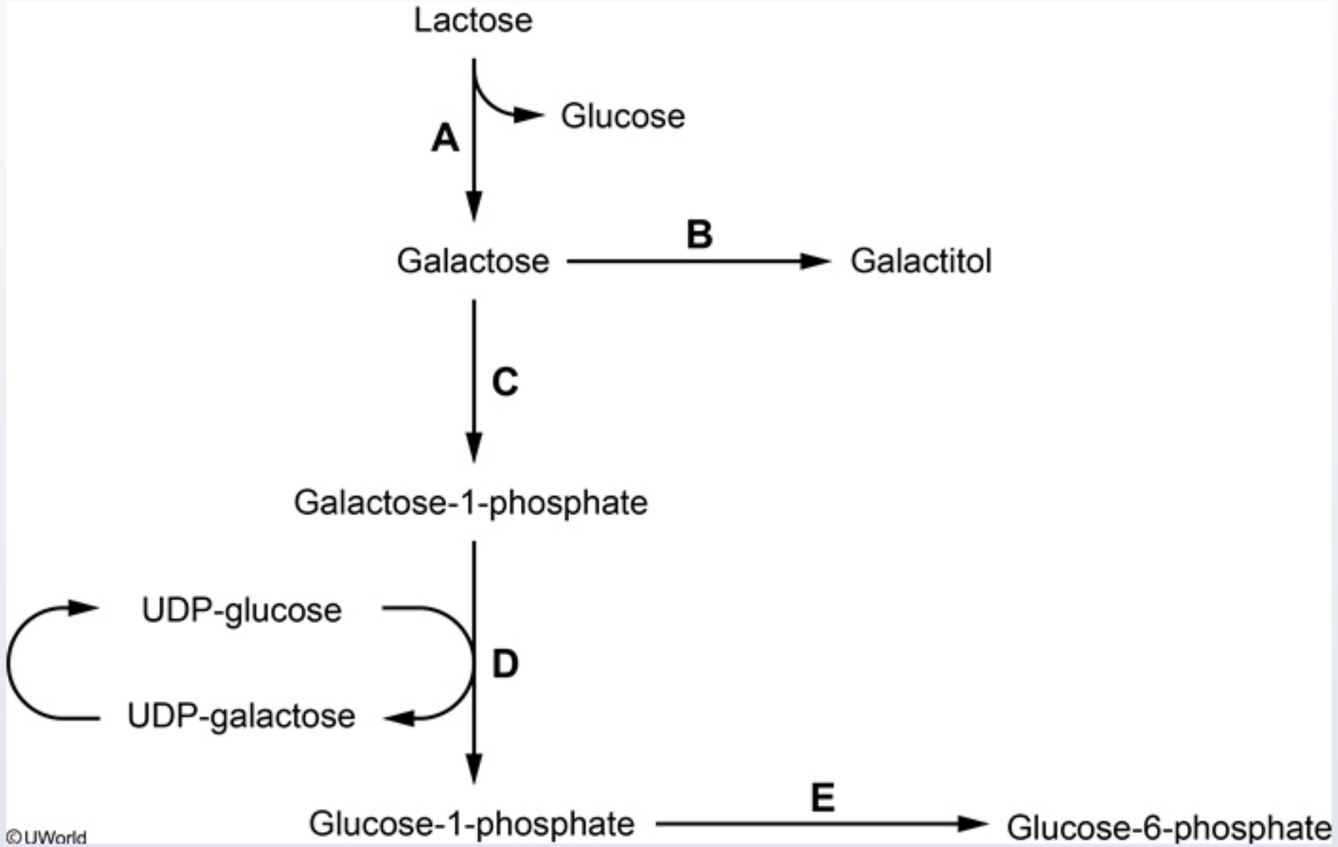

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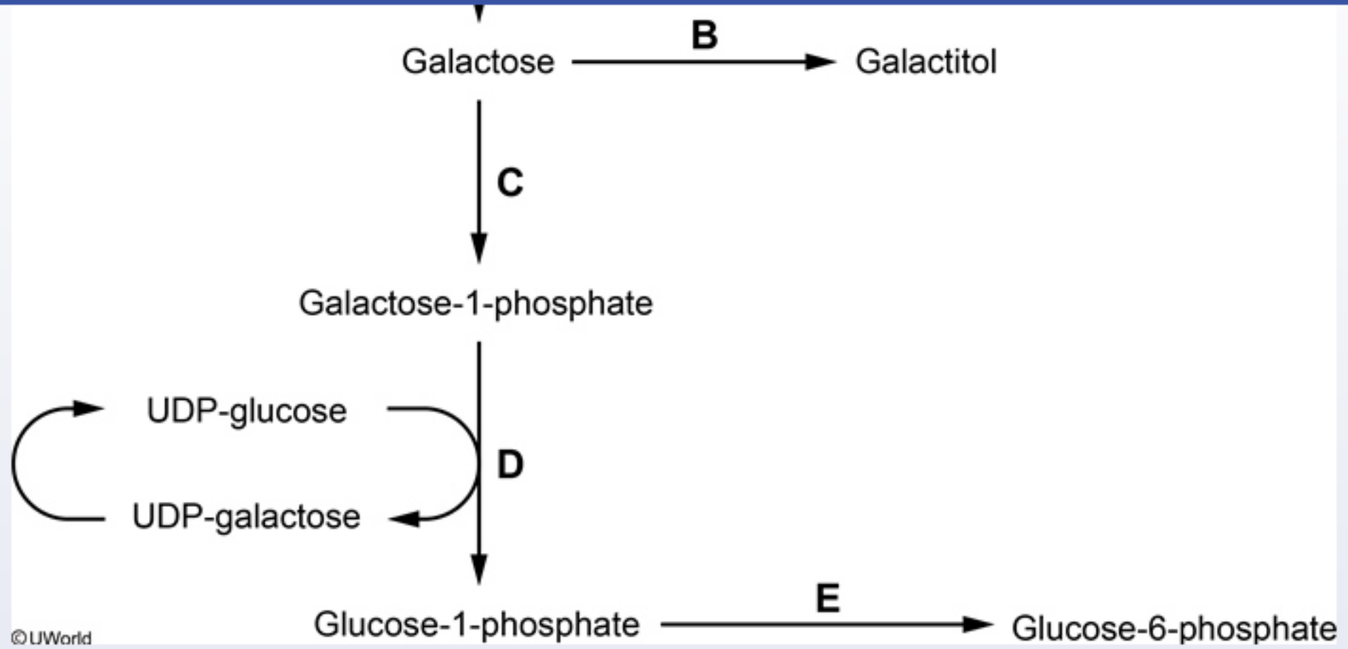

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D. D
E. E

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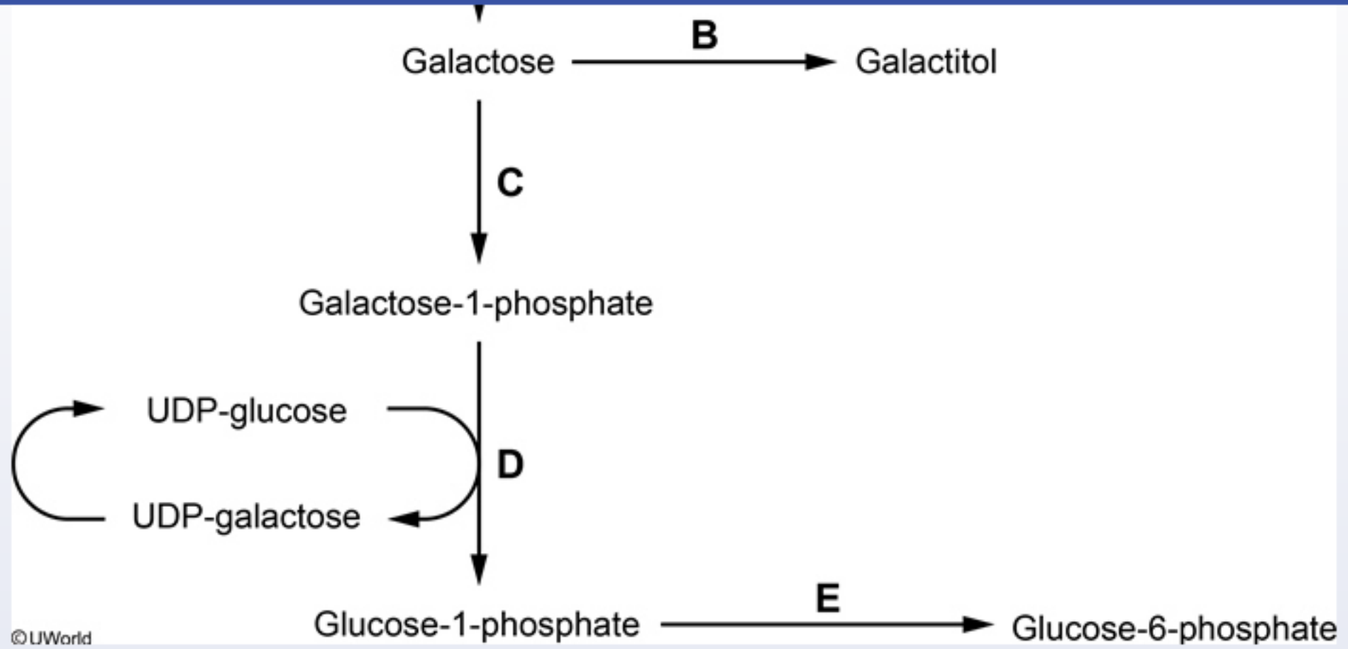

A. A (16%)
B. B (3%)
C. C (11%)
✓ D. D (58%)
E. E (10%)

Omitted
Correct answer

58%
Answered correctly

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Time Spent

06/04/2020
Last Updated

Clinically relevant disorders of galactose metabolism	
Enzyme	**Clinical features**
Galactose-1-phosphate uridyl transferase	Jaundice, vomiting, hepatomegaly, renal dysfunction (aminoaciduria, hyperchloremic metabolic acidosis) *Escherichia coli* sepsis, cataract, hemolytic anemia
Galactokinase	Cataracts, rarely pseudotumor cerebri (galactitol accumulation)

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Lactose (milk sugar) is degraded by lactase, the intestinal disaccharidase, to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme galactokinase (GALK). Galactose-1-phosphate is converted to glucose-1-phosphate by epimerization with transfer of uridine diphosphate (UDP) from UDP-glucose to UDP-galactose. This reaction is catalyzed by **galactose-1-phosphate uridyl transferase (GALT)**. UDP-galactose is then epimerized to UDP-glucose by UDP-galactose-4 epimerase. Although GALT deficiency is the most common form, a defect in any of these three enzymes can cause galactosemia.

Galactosemia can present with **vomiting** and lethargy soon after initiation of **breastfeeding**. In GALT deficiency, toxicity of accumulated galactose-1-phosphate is responsible for impaired liver function (transaminitis, hyperbilirubinemia, hypoglycemia) and renal dysfunction (hyperchloremic metabolic acidosis, aminoaciduria). Patients are also predisposed to *Escherichia coli* (gram-negative rod) **sepsis**.

Restricting lactose intake (eg, breast milk) and initiation of soy milk-based formula can result in regression of cataracts and improvement in renal and liver function. Soy milk consists of sucrose, which is metabolized to glucose and fructose. Glucose and fructose do not need GALT or GALK to enter the glycolytic pathway and generate energy.

(Choice A) Lactase hydrolyzes lactose to galactose in the small intestine. Primary lactase deficiency causes lactose intolerance and is rare in neonates.

Lactose (milk sugar) is degraded by lactase, the intestinal disaccharidase, to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme galactokinase (GALK). Galactose-1-phosphate is converted to glucose-1-phosphate by epimerization with transfer of uridine diphosphate (UDP) from UDP-glucose to UDP-galactose. This reaction is catalyzed by **galactose-1-phosphate uridyl transferase (GALT)**. UDP-galactose is then epimerized to UDP-glucose by UDP-galactose-4 epimerase. Although GALT deficiency is the most common form, a defect in any of these three enzymes can cause galactosemia.

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(Choice A) Lactase hydrolyzes lactose to galactose in the small intestine. Primary lactase deficiency causes lactose intolerance and is rare in neonates.

(Choice B) Aldose reductase converts galactose to galactitol. GALT and GALK deficiency can lead to galactitol accumulation in the lens, which can lead to **cataract** formation in patients with galactosemia. However, aldose reductase deficiency does not cause galactosemia.

(Choice C) GALK phosphorylates galactose and its deficiency typically causes less severe manifestations of galactosemia with cataract formation (due to galactitol) being the most common manifestation. Because galactose-1-phosphate does not accumulate, liver and renal functions are preserved.

(Choice E) Phosphoglucomutase isomerizes glucose-1-phosphate to glucose-6-phosphate, which then enters the glycolytic pathway. Its deficiency is rare. In GALT deficiency, accumulation of galactose-1-phosphate blocks phosphoglucomutase, thereby preventing energy production via glycolysis.

Educational objective:
Classic galactosemia results from deficiency of galactose-1-phosphate uridyl transferase. Clinical features include vomiting, lethargy, jaundice, and *Escherichia coli* sepsis. Cessation of breastfeeding and switching to soy milk-based formula is recommended.

(hyperchloremic metabolic acidosis, aminoaciduria). Patients are also predisposed to *Escherichia coli* (gram negative rod) **sepsis**.

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References

- Galactosemia: when is it a newborn screening emergency?

Biochemistry	Gastrointestinal & Nutrition	Galactosemia
Subject	System	Topic

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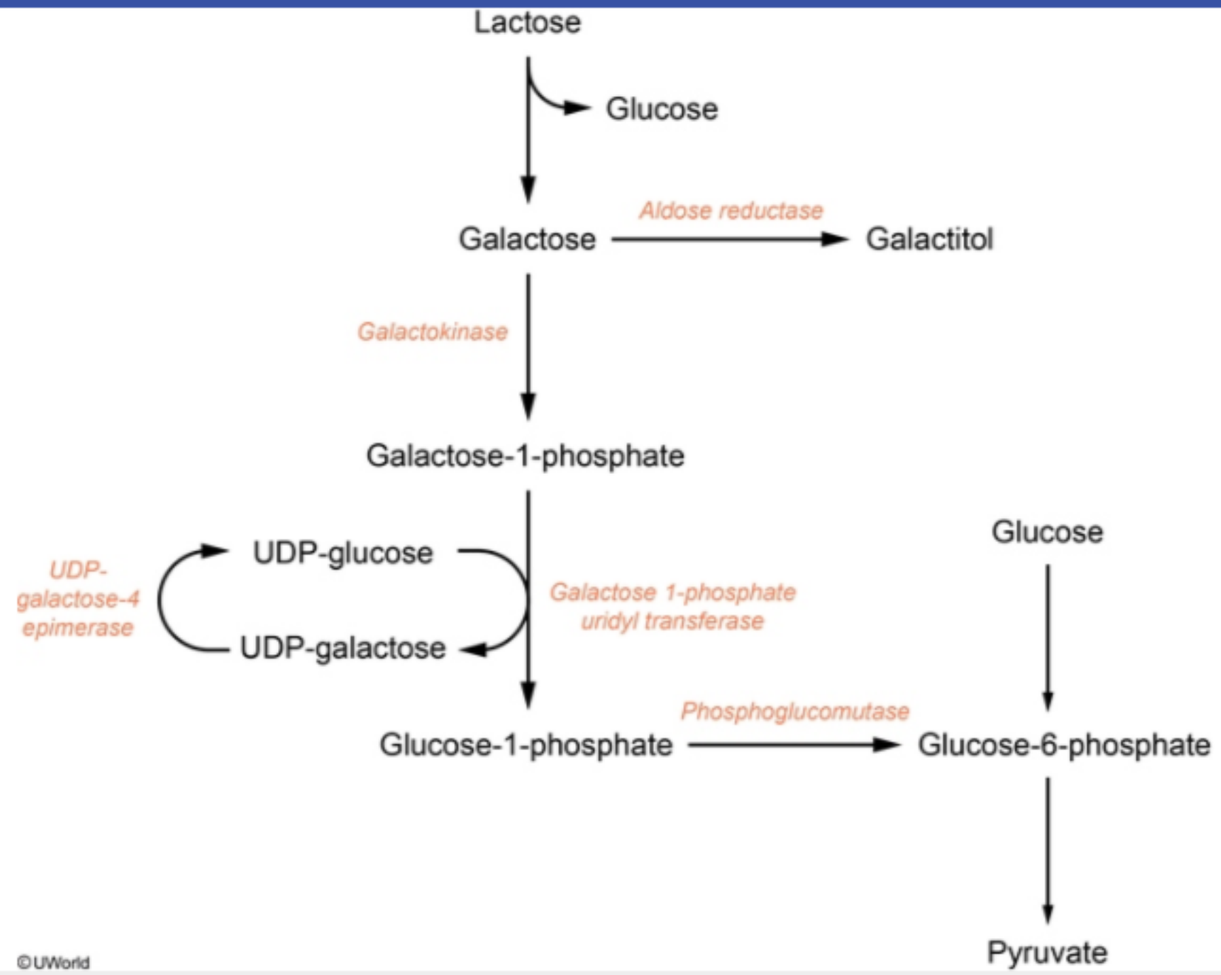
Clinically relevant disorders of galactose metabolism

Exhibit Display



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(Choice B) Aldose reductase converts galactose to galactitol. GALT and GALK deficiency can lead to galactitol accumulation in the lens, which

A 56-year-old man comes to the office due to difficulty swallowing for the past several months. He has the most trouble with solid foods and says, "They seem to get stuck in my throat if I don't chew a lot." The patient has no chest pain or heartburn and has lost 4.5 kg (10 lb) in the last 3 months. He has been an avid hunter for many years and frequently cures the meat he eats with sodium nitrite. Physical examination is unremarkable. Endoscopy shows an ulcerated mass in the distal third of the esophagus, and biopsy samples are obtained from the mass and adjacent normal mucosa. Analysis of the samples shows accelerated cytosine deamination of chromosomal DNA in both normal and malignant epithelial cells. This damage is most likely to be repaired through which of the following enzymatic sequences?

A. Endonuclease, polymerase, glycosylase, lyase, ligase

B. Endonuclease, polymerase, lyase, glycosylase, ligase

C. Glycosylase, endonuclease, lyase, polymerase, ligase

D. Glycosylase, ligase, lyase, endonuclease, polymerase

E. Lyase, endonuclease, glycosylase, polymerase, ligase

Submit

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- A. Endonuclease, polymerase, glycosylase, lyase, ligase (15%)
- B. Endonuclease, polymerase, lyase, glycosylase, ligase (23%)
- ✓ C. Glycosylase, endonuclease, lyase, polymerase, ligase (44%)
- D. Glycosylase, ligase, lyase, endonuclease, polymerase (1%)
- E. Lyase, endonuclease, glycosylase, polymerase, ligase (14%)

Omitted
Correct answer
C

44%
Answered correctly

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Last Updated

Explanation

Base excision repair

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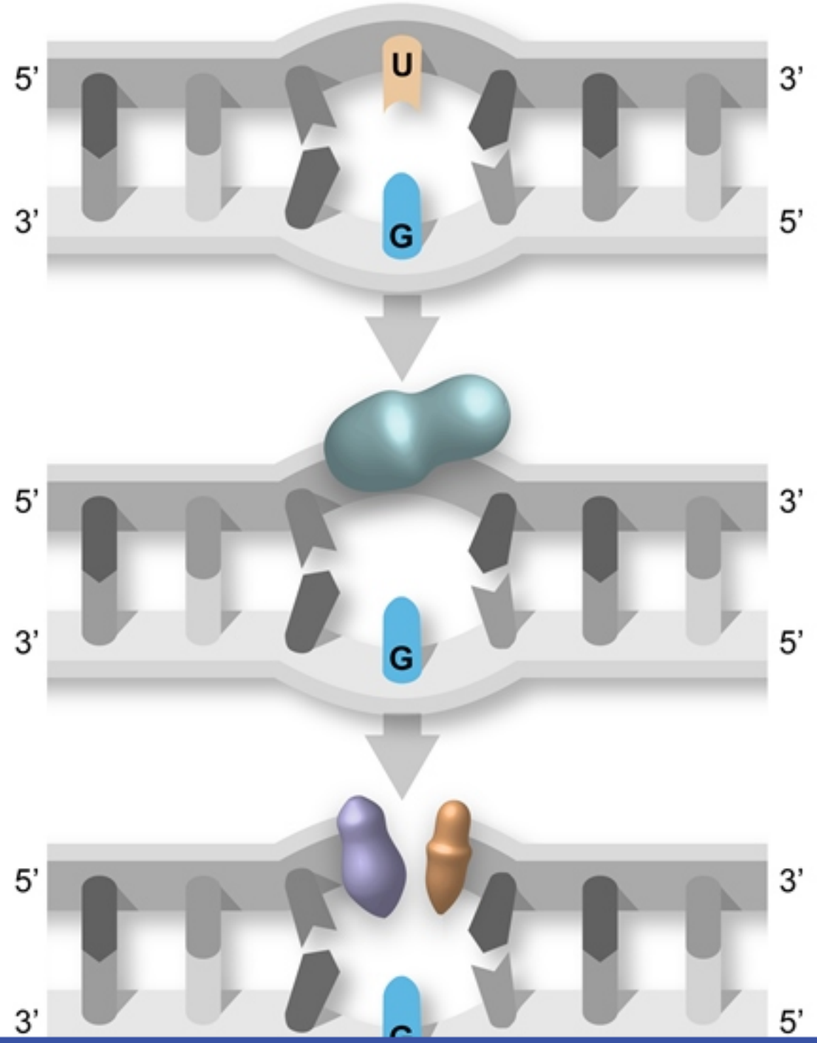
Base excision repair



Cytosine deamination creates unusual base **uracil**

Glycosylase cleaves the altered base leaving an AP site

Endonuclease cleaves the 5' end and **lyase** cleaves the 3' sugar-phosphate

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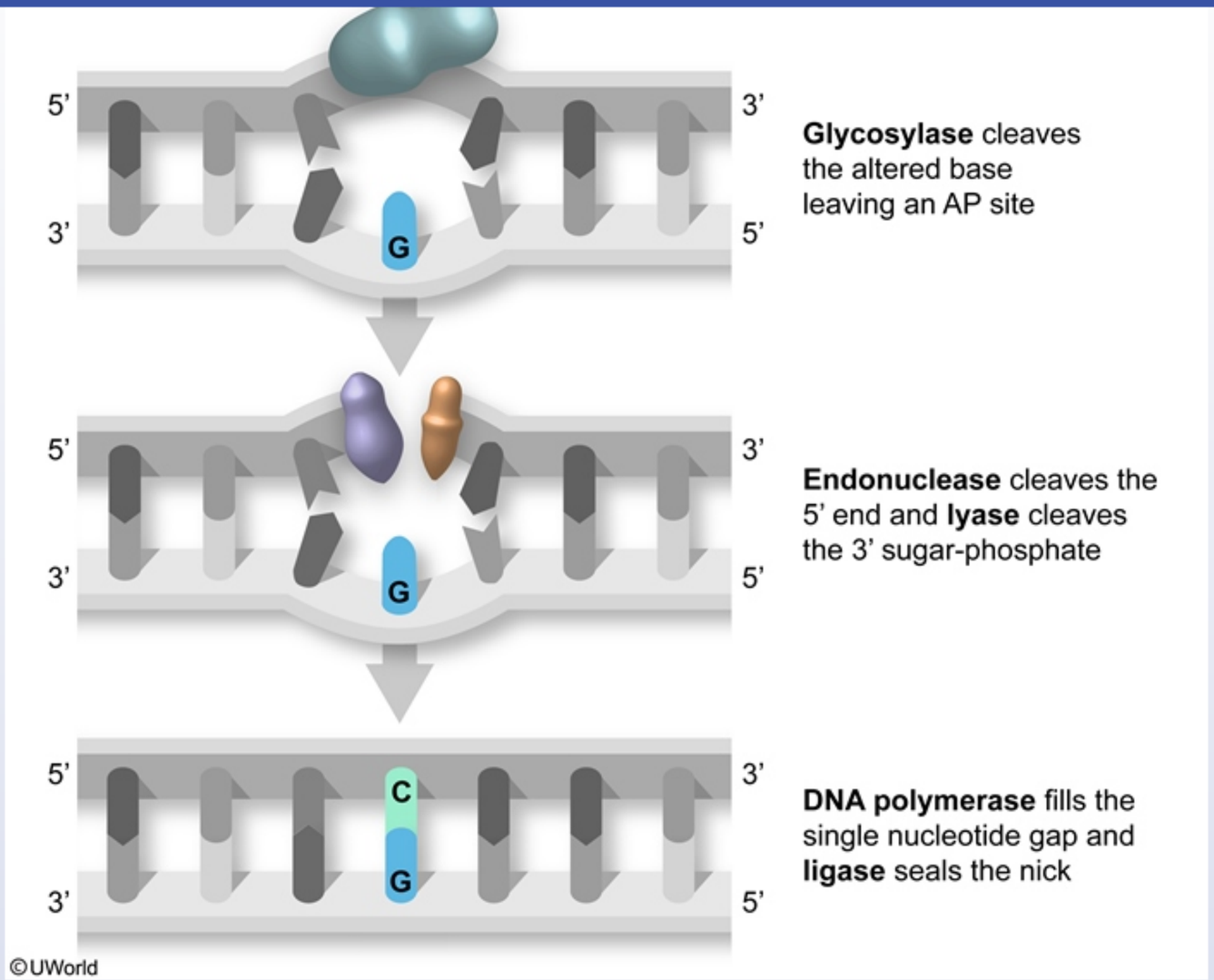
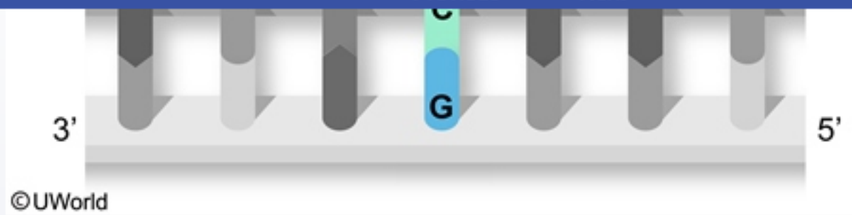


Base excision repair is responsible for repairing various non-bulky DNA base alterations, including depurination, alkylation, oxidation, and deamination. Excessive consumption of **dietary nitrites** can promote the deamination of cytosine, adenine, and guanine to form uracil,



DNA polymerase fills the single nucleotide gap and **ligase** seals the nick

Base excision repair is responsible for repairing various non-bulky DNA base alterations, including depurination, alkylation, oxidation, and deamination. Excessive consumption of **dietary nitrites** can promote the deamination of cytosine, adenine, and guanine to form uracil, hypoxanthine, and xanthine, respectively. If these abnormal bases are not removed and replaced with the correct base, DNA mutations and **carcinogenesis** may result.

Base excision repair (not to be confused with nucleotide excision repair or mismatch repair) begins with recognition of abnormal bases by specific **glycosylases**. These cleave the altered DNA bases from the parent DNA molecule, leaving an empty sugar-phosphate site called an apurinic/apyrimidinic site (AP). An **endonuclease** then cleaves the 5' end of the AP site before a **lyase** (or phosphodiesterase) enzyme subsequently completes extraction of the AP site from the DNA molecule by removing the remaining sugar-phosphate group. **DNA polymerase** then fills the gap with the correct sugar-phosphate base, and the final nick is sealed by **ligase**.

Educational objective:

Base excision repair is used to correct single-base DNA defects induced spontaneously or by exogenous chemicals. In this process, glycosylases remove the defective base, and the corresponding empty sugar-phosphate site is cleaved and removed by the action of endonuclease and lyase. DNA polymerase then replaces the missing nucleotide, and ligase seals the final remaining nick.

References

- Overview of base excision repair biochemistry.

Biochemistry	Gastrointestinal & Nutrition	Dna structure & function
Subject	System	Topic

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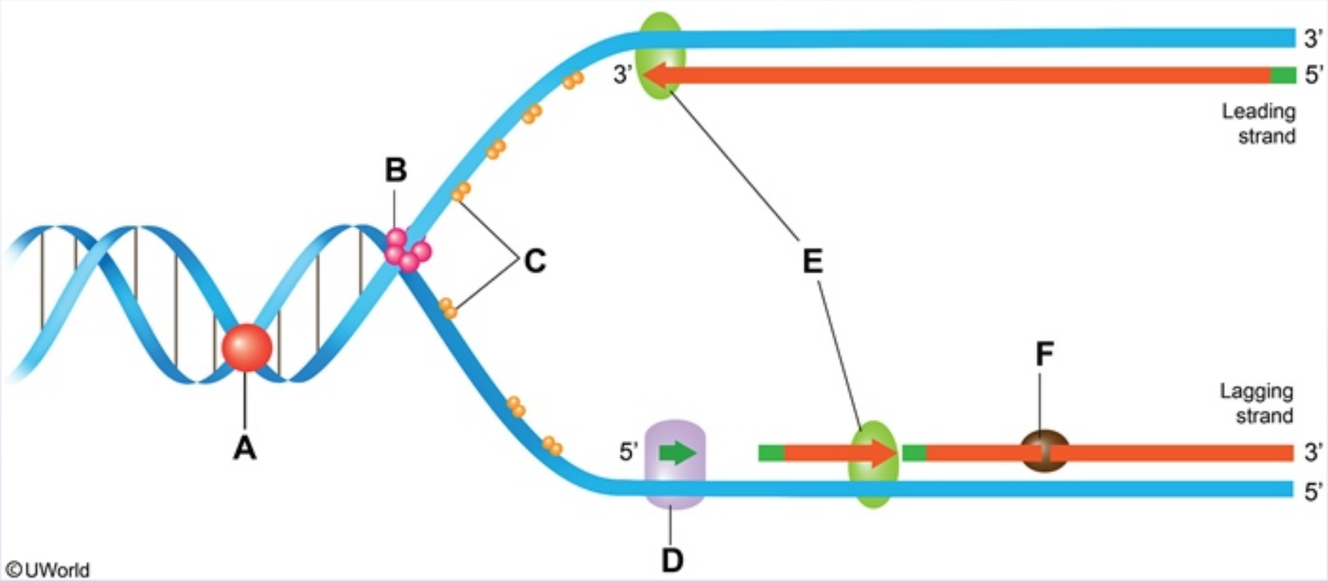
A 13-year-old boy with growth retardation, microcephaly, sun-sensitive skin rash, and recurrent infections is being evaluated for a possible inherited genetic defect. The patient is the second-born child of a first cousin marriage. His parents and siblings are healthy, but 2 of his maternal cousins have similar signs and symptoms. Genetic analysis of the patient reveals a defect in the *BLM* gene that codes for DNA helicase. Which of the following is the most likely site of action of this enzyme in the DNA replication fork shown below?



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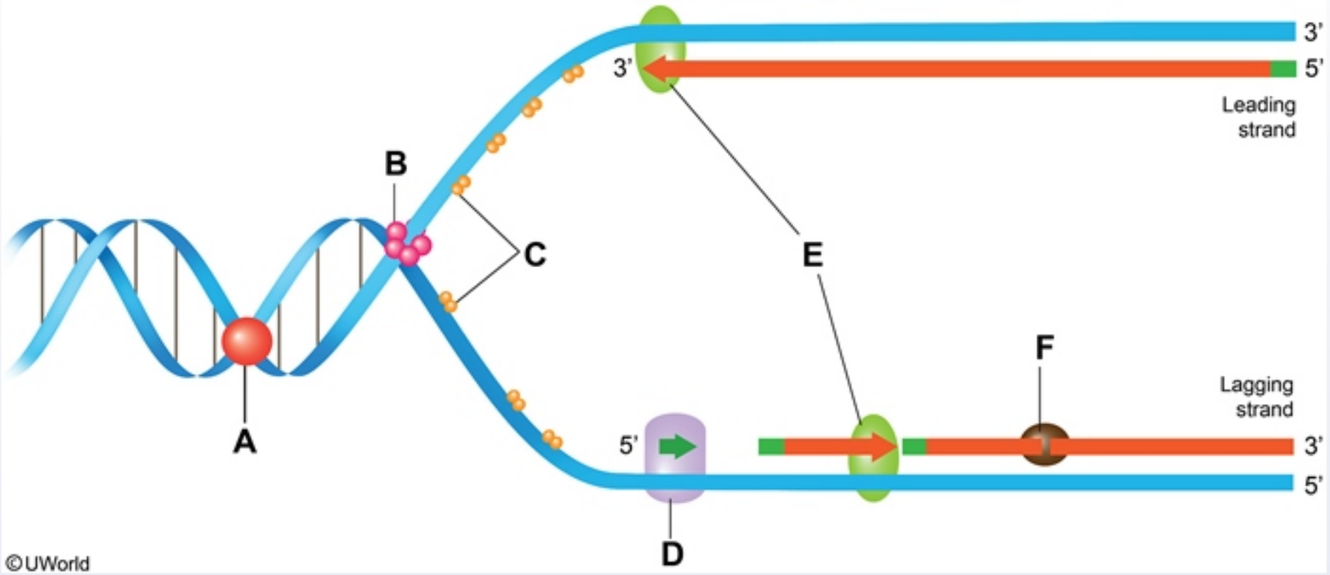

A. A
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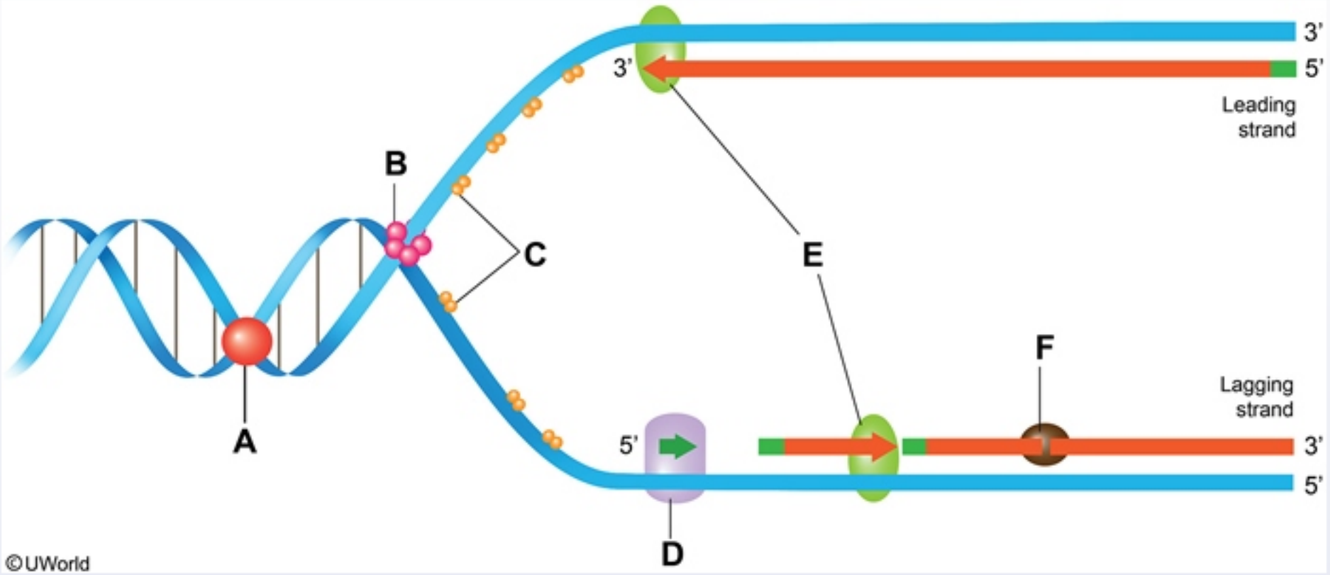

A. A (6%)
✓ B. B (86%)
C. C (4%)
D. D (0%)
E. E (0%)
F. F (0%)

Omitted
Correct answer

86%
Answered correctly

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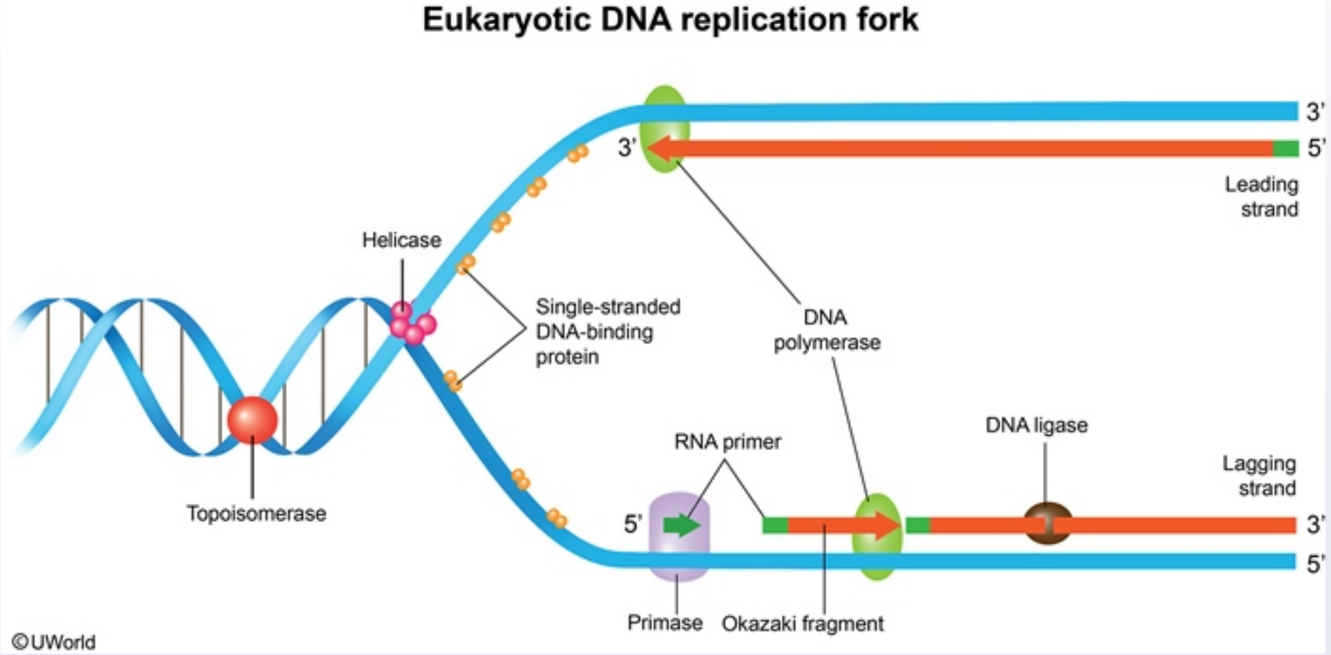
01/16/2020
Last Updated

Explanation



This patient has **Bloom syndrome**, a rare autosomal recessive disorder caused by mutations in the *BLM* gene. This gene encodes DNA helicase, an enzyme responsible for unwinding of the double helix during DNA replication and repair. **Helicase dysfunction** results in chromosomal instability and breakage and manifests clinically with **growth retardation, facial anomalies** (eg, microcephaly), **photosensitive rash,** and **immunodeficiency** (eg, recurrent infections).

DNA replication occurs during the S phase (synthesis phase) of the cell cycle and is coordinated by the effects of multiple proteins. First, the origin of replication is identified and bound by a multi-subunit protein (the origin recognition complex), which locally dissociates double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA). ssDNA-binding proteins then bind to and stabilize the ssDNA, preventing it from reannealing **(Choice C)**.

Helicase subsequently binds to ssDNA at the origin of replication, moves into the replication fork, and proceeds to separate and unwind the

origin of replication is identified and bound by a multi-subunit protein (the origin recognition complex), which locally dissociates double-stranded DNA (dsDNA) into single-stranded DNA (ssDNA). ssDNA-binding proteins then bind to and stabilize the ssDNA, preventing it from reannealing **(Choice C)**.

Helicase subsequently binds to ssDNA at the origin of replication, moves into the replication fork, and proceeds to separate and unwind the dsDNA. As DNA is unwound, superhelical tension is generated as supercoils are being formed. Topoisomerase relieves this tension by introducing transient single- or double-stranded nicks in the DNA. This enzyme is located ahead of helicase on the dsDNA segment of the replication fork **(Choice A)**.

(Choice D) Before DNA polymerase can begin synthesizing DNA, it requires an RNA primer made up of short RNA sequences base-paired to the parent DNA. This primer is synthesized by the enzyme primase (DNA-dependent RNA polymerase).

(Choice E) DNA polymerase synthesizes new daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.

(Choice F) Okazaki fragments are ultimately bound together by the enzyme ligase.

Educational objective:
Bloom syndrome is a rare autosomal recessive condition caused by mutations in the *BLM* gene encoding helicase, an enzyme that unwinds the double helix during DNA replication. Patients typically present with growth retardation, facial anomalies, photosensitive skin rash, and immunodeficiency due to chromosomal instability and breakage.

References

- Clinical features of Bloom syndrome and function of the causative gene, BLM helicase.
- The replication fork: understanding the eukaryotic replication machinery and the challenges to genome duplication.

Biochemistry	General Principles	Dna replication
Subject	System	Topic

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A 2-year-old boy is being evaluated for failure to thrive and developmental delay. His past medical history is significant for recurrent ear infections since age 6 months. Physical examination shows coarse facial features, corneal clouding, hepatosplenomegaly, and restricted joint mobility. Mass spectrometry analysis is performed on cultured fibroblasts and reveals deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. Normally, these proteins are most likely to be transported to which of the following cellular locations?

A. Extracellular space
B. Lysosome
C. Mitochondria
D. Nucleus
E. Plasma membrane

Submit

A 2-year-old boy is being evaluated for failure to thrive and developmental delay. His past medical history is significant for recurrent ear infections since age 6 months. Physical examination shows coarse facial features, corneal clouding, hepatosplenomegaly, and restricted joint mobility. Mass spectrometry analysis is performed on cultured fibroblasts and reveals deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. Normally, these proteins are most likely to be transported to which of the following cellular locations?

- A. Extracellular space (8%)
- ✓ B. Lysosome (77%)
- C. Mitochondria (2%)
- D. Nucleus (0%)
- E. Plasma membrane (11%)

Omitted
Correct answer
B

77%
Answered correctly

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Last Updated

Explanation

This patient has **inclusion cell (I-cell) disease**, an autosomal recessive lysosomal storage disorder. I-cell disease occurs due to defects in **protein targeting**, a process by which proteins are transported to their appropriate intra- or extracellular location. Post-translational modifications (eg, folding, glycosylation, and phosphorylation) often function as markers that help guide the protein to its final destination.

Proteins targeted for **lysosomes** are modified differently than those destined for extracellular secretion. A Golgi body **phosphotransferase enzyme** catalyzes the **phosphorylation of mannose residues** on lysosome-bound proteins, allowing them to traverse the Golgi network and

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Proteins targeted for **lysosomes** are modified differently than those destined for extracellular secretion. A Golgi body **phosphotransferase enzyme** catalyzes the **phosphorylation of mannose residues** on lysosome-bound proteins, allowing them to traverse the Golgi network and ultimately be transported to the lysosome, where they serve as catalysts for degradation of cellular components.

A defective phosphotransferase enzyme causes extracellular secretion of these proteins and accumulation of cellular debris in the lysosome, forming the characteristic inclusion bodies seen in I-cell disease. Patients with this disorder typically present with failure to thrive and cognitive deficits in the first year of life along with characteristic physical features (eg, coarse facial features, corneal clouding). I-cell disease is typically fatal in childhood.

(Choice A) Following translation in the endoplasmic reticulum, secretory proteins traverse the Golgi apparatus and are packaged into vesicles that ultimately fuse with the plasma membrane, facilitating extracellular protein secretion.

(Choice C) Most mitochondrial proteins are synthesized in the cytosol and contain specific mitochondrial targeting sequences. Translocases detect these sequences and shuttle the proteins into and between the different mitochondrial compartments.

(Choice D) In order for nuclear proteins to be imported into the nucleus, they must first present a nuclear localization signal to nuclear pore complexes located on the nuclear envelope. A different nuclear export signal is required for proteins to leave the nucleus.

(Choice E) Peripheral membrane proteins may be modified through a lipidation process in which a hydrophobic lipid anchor is covalently attached to the protein. This process facilitates protein interaction with the cell membrane.

Educational objective:
Protein targeting is the process by which proteins with different intra- and extracellular fates reach their destination. Proteins destined for the lysosome require phosphorylation of specific mannose residues to ensure proper transit through the Golgi apparatus.

References

- Mannose-6-phosphate pathway: a review on its role in lysosomal function and dysfunction

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References

- Mannose-6-phosphate pathway: a review on its role in lysosomal function and dysfunction

Biochemistry	General Principles	Lysosomal storage disorder
Subject	System	Topic

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A 54-year-old woman is evaluated for progressive constipation, anorexia, and a 5.4-kg (12-lb) weight loss over the past several months. Physical examination is unremarkable. Stool guaiac test is positive, and a colonoscopy is performed. An exophytic mass is identified in the sigmoid colon. The patient undergoes a left hemicolectomy, and histopathology of the surgical specimen is positive for adenocarcinoma. Molecular testing of the cancer cells reveals a mutation in the *KRAS* gene that results in constitutive activation of the Ras protein. Under normal circumstances, this protein is only active when bound to which of the following substances?

A. ATP
B. Ca^{2+}
C. cAMP
D. GTP
E. IP_3

Submit

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- A. ATP (13%)
- B. Ca^{2+} (7%)
- C. cAMP (15%)
- ✓ D. GTP (55%)
- E. IP_3 (8%)

Omitted
Correct answer
D

55%
Answered correctly

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03/25/2020
Last Updated

Explanation

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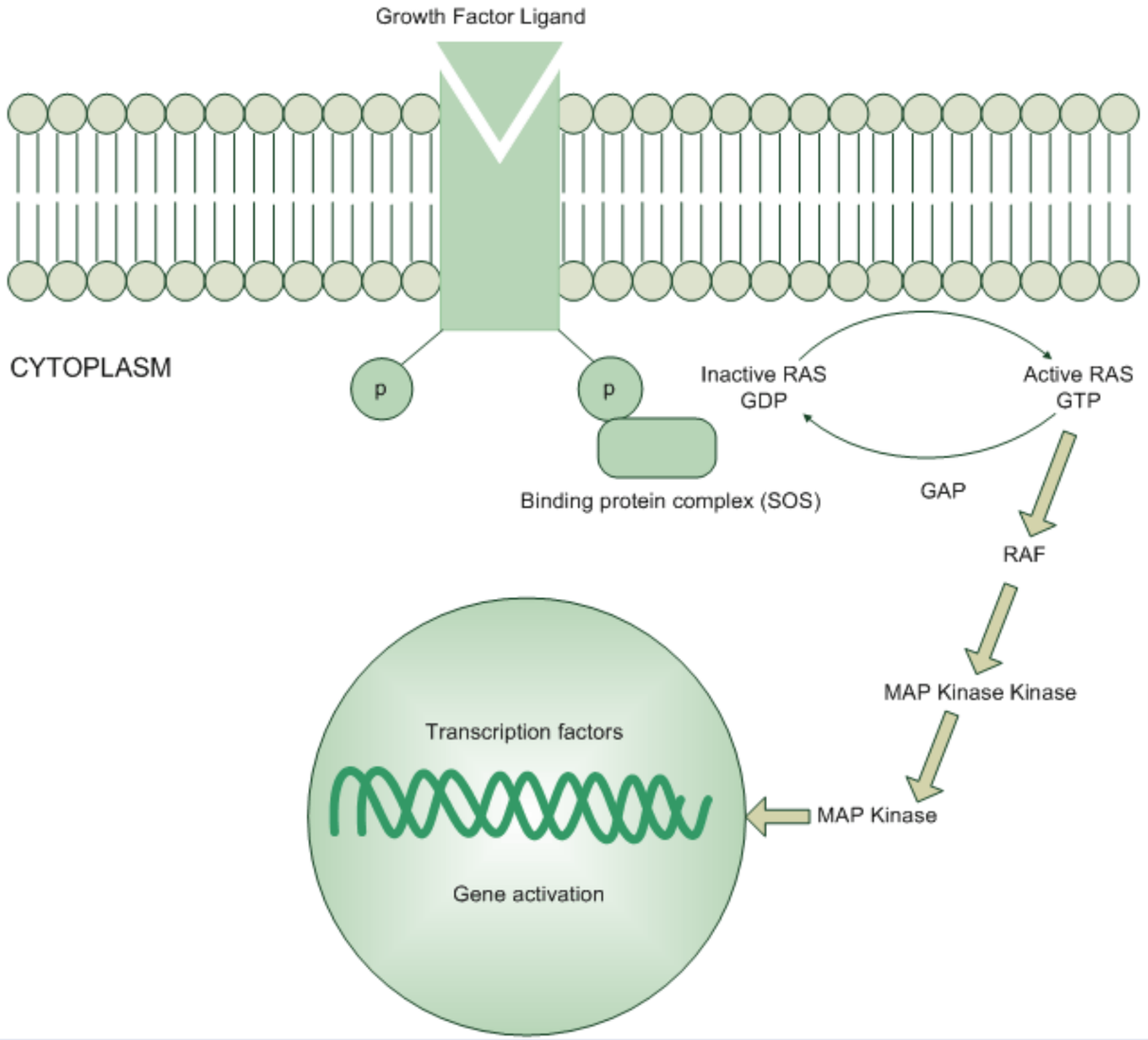

RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras proteins exist in 2 different states:

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras proteins exist in 2 different states: an **inactive GDP-bound state** and an **active GTP-bound state**. Ras becomes activated when a growth factor ligand binds to a **receptor tyrosine kinase** located on the cell membrane, causing autophosphorylation of the receptor. This triggers binding of adaptor proteins that interact with Ras, promoting GDP removal and GTP binding. Activated Ras then begins a phosphorylation cascade that results in the activation of **mitogen-activated protein kinase (MAPK)**, which enters the nucleus to influence gene transcription.

Ras proteins have intrinsic GTPase activity that allows them to hydrolyze GTP; this mechanism prevents accumulation of active Ras (GTP-bound) in the absence of hormonal signaling. *RAS* gene mutations can lead to decreased intrinsic GTPase activity; this results in a constitutively activated Ras protein that causes constant and unregulated cell proliferation. *RAS* mutations are commonly identified in cancerous tumors, specifically colorectal and pancreatic malignancies.

(Choices A and C) ATP serves as a phosphate source for kinase-dependent phosphorylation reactions involved in numerous intracellular signaling pathways. It is also used as a substrate to produce cyclic AMP (cAMP) in the cAMP second messenger system.

(Choice B) Ca^{2+} is important for cell signaling as its intracellular presence alters the function of many proteins and enzymes. Ca^{2+} is required for many basic physiologic activities including apoptosis, muscular contraction, and neuronal transmission.

(Choice E) IP_3 is the water-soluble component of the IP_3/DAG second messenger system. IP_3 acts on the endoplasmic reticulum to cause intracellular Ca^{2+} release while DAG remains in the cell membrane and activates membrane-bound protein kinases.

Educational objective:
Regulation of the Ras-MAPK signal transduction pathway requires a balance between active (GTP-bound) and inactive (GDP-bound) Ras proteins. *RAS* gene mutations, which result in constitutively activated Ras proteins, are implicated in the development of malignant tumors.

References

- MEK inhibitors: a therapeutic approach to targeting the Ras-MAP kinase pathway in tumors.

Biochemistry	Gastrointestinal & Nutrition	Colorectal cancer
Subject	System	Topic

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A research scientist develops an agent that specifically blocks the interaction of inositol triphosphate with its intracellular receptor. A study is then performed in which vascular smooth muscle cells are divided into 2 groups: an experimental group treated with the receptor blocker and an untreated control group. Both groups are exposed to phenylephrine. Compared to the control cells, decreased activity of which of the following enzymes is most likely to be observed in the experimental cells?

A. Adenylate cyclase
B. Lipoxygenase
C. Phosphodiesterase
D. Phospholipase C
E. Protein kinase C

Submit

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- A. Adenylate cyclase (9%)
- B. Lipoxygenase (0%)
- C. Phosphodiesterase (4%)
- D. Phospholipase C (36%)
- ✓ E. Protein kinase C (49%)

Omitted
Correct answer
E

49%
Answered correctly

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Last Updated

Explanation

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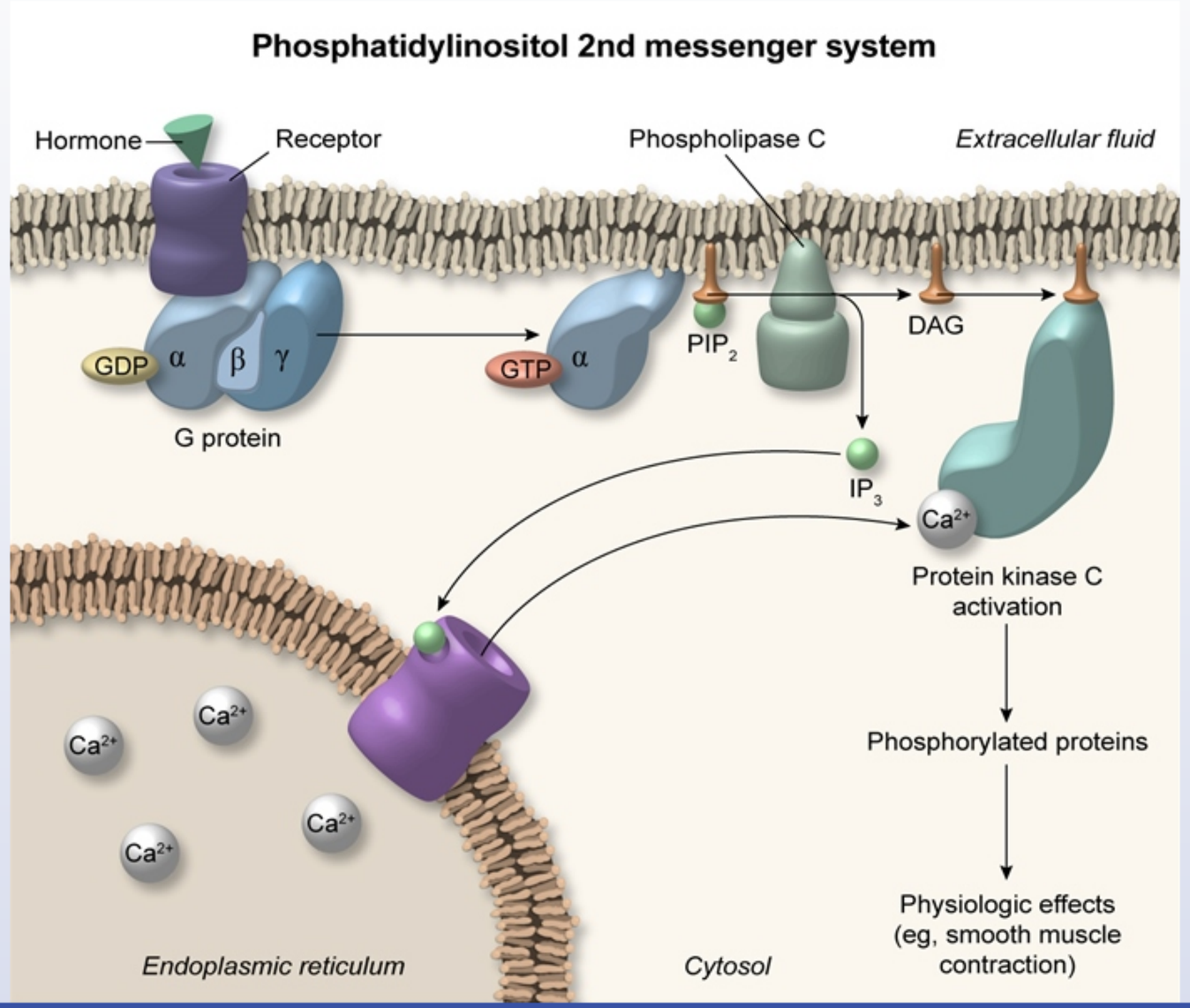

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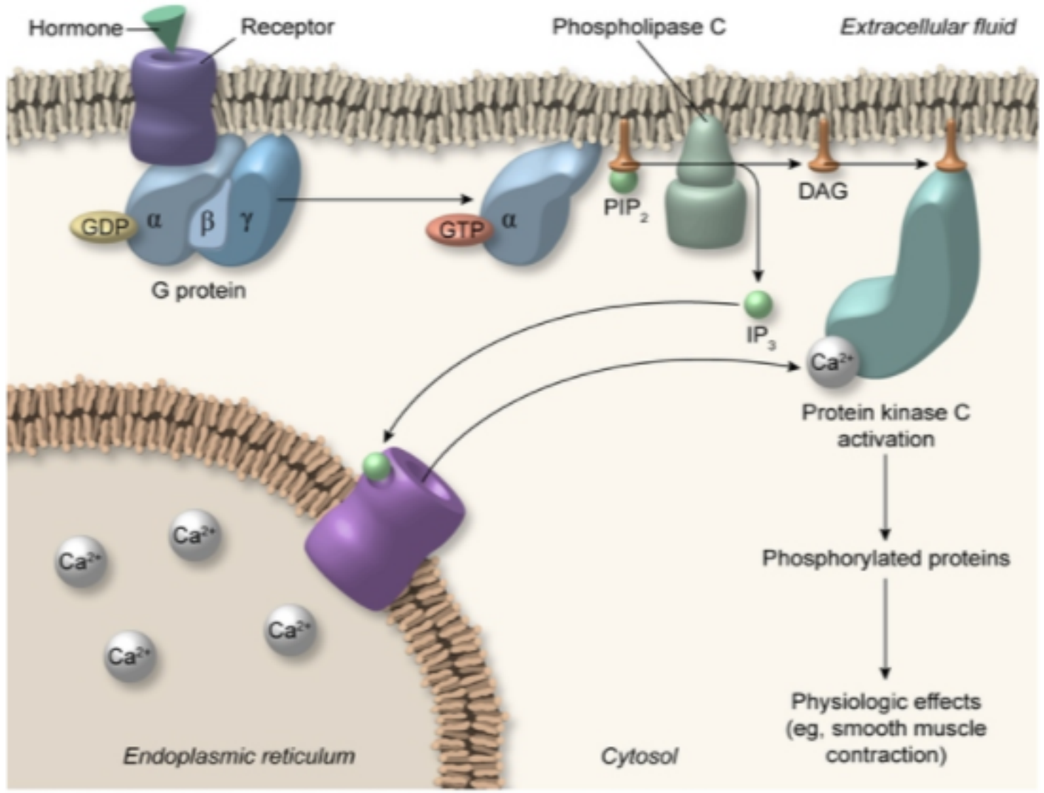
Phosphatidylinositol 2nd messenger system



DAG = diacylglycerol; **GDP** = guanosine 5'-diphosphate; **GTP** = guanosine 5'-triphosphate; **IP_3** = inositol 1,4,5-trisphosphate; **PIP_2** = phosphatidylinositol 4,5-bisphosphate.

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G protein-coupled receptors have a characteristic structure with 7 transmembrane regions, an extracellular domain, and an intracellular domain

G protein-coupled receptors have a characteristic structure with 7 transmembrane regions, an extracellular domain, and an intracellular domain coupled with a G protein. In their inactivated state, G proteins exist as heterotrimers consisting of alpha, beta, and gamma subunits with GDP tightly bound to the alpha subunit. G proteins are activated after **ligand binding to the extracellular domain** of the receptor. The first step in activation occurs when GDP is exchanged for GTP on the alpha subunit. Once bound to GTP, the alpha subunit dissociates from the beta and gamma subunits and activates either adenylate cyclase or phospholipase C, depending on the ligand.

When phenylephrine binds to an alpha-1 receptor on vascular smooth muscle cells, the alpha subunit of the G protein (G_q) **activates phospholipase C**, which breaks down phosphatidylinositol bisphosphate into inositol triphosphate (IP_3) and diacylglycerol (DAG). DAG stimulates protein kinase C, which phosphorylates downstream intracellular proteins to produce its physiologic effects (eg, smooth muscle contraction). **IP_3** produces most of its effects by **increasing intracellular calcium**, which also **activates protein kinase C**. In the study described above, protein kinase C activity would be reduced in the experimental group compared to the control group as calcium release from the endoplasmic reticulum is interrupted.

(Choice A) Activation of adenylate cyclase leads to the formation of cAMP and subsequent activation of protein kinase A. Protein kinase A phosphorylates intracellular proteins to produce its effects.

(Choice B) Lipoxygenase is an enzyme responsible for the formation of leukotrienes from arachidonic acid. It is not directly involved in the phosphatidylinositol second messenger system.

(Choice C) Phosphodiesterase is an enzyme that terminates the effects of ligands that act via cAMP or cGMP second messenger systems. It has no direct effect on the phosphatidylinositol second messenger system.

(Choice D) The activity of phospholipase C would be unchanged if IP_3 were blocked because phospholipase C exerts its effect before IP_3 in the phosphatidylinositol second messenger system.

Educational objective:
After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol (DAG) and inositol triphosphate (IP_3). Protein kinase C is subsequently activated by DAG and calcium; the latter is released from the endoplasmic reticulum under the influence of IP_3.

References

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After a ligand binds to a G protein-coupled receptor that activates phospholipase C, membrane phospholipids are broken down into diacylglycerol (DAG) and inositol triphosphate (IP_3). Protein kinase C is subsequently activated by DAG and calcium; the latter is released from the endoplasmic reticulum under the influence of IP_3.

References

- G protein-dependent regulation of phospholipase C by cell surface receptors.
- Role of inositol lipid breakdown in the generation of intracellular signals. State of the art lecture.

Biochemistry	General Principles	Second messengers
Subject	System	Topic

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A research scientist purifies DNA polymerase III from *Escherichia coli* extract. When the enzyme is incubated in a mixture containing DNA templates, RNA primer oligonucleotides, and tagged deoxynucleotides, she finds that the enzyme possesses 3' to 5' exonuclease activity. Which of the following enzymatic actions was most likely observed during the experiment?

A. Cleavage of DNA strands to remove supercoils

B. Excision of thymine dimers within DNA

C. Removal of mismatched base pairs during DNA replication

D. Removal of RNA primer nucleotides

E. Unwinding of the 2 strands of template DNA

Submit

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- A. Cleavage of DNA strands to remove supercoils (1%)
- B. Excision of thymine dimers within DNA (4%)
- ✓ C. Removal of mismatched base pairs during DNA replication (70%)
- D. Removal of RNA primer nucleotides (21%)
- E. Unwinding of the 2 strands of template DNA (2%)

Omitted
Correct answer
C

70%
Answered correctly

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Last Updated

Explanation

Proteins & their function in prokaryotic DNA replication	
Helicase	Unwinding of double helix
Topoisomerase II	Removal of supercoils

Proteins & their function in prokaryotic DNA replication	
Helicase	Unwinding of double helix
Topoisomerase II (DNA gyrase)	Removal of supercoils
Single-stranded DNA-binding protein	Stabilization of unwound template strands
Primase (RNA polymerase)	Synthesis of RNA primer
DNA polymerase III	5' to 3' DNA synthesis & 3' to 5' exonuclease ("proofreading") activity
DNA polymerase I	Same as DNA polymerase III Also removes RNA primer (5' to 3' exonuclease activity) & replaces it with DNA
DNA ligase	Joining of Okazaki fragments (lagging strand)

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DNA replication is coordinated by the actions of multiple enzymes and proteins and requires a high degree of fidelity to ensure preservation of the genetic code in daughter cells.

DNA polymerases are the primary enzymes responsible for DNA synthesis. Prokaryotes such as *Escherichia coli* have 3 major types of DNA

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DNA replication is coordinated by the actions of multiple enzymes and proteins and requires a high degree of fidelity to ensure preservation of the genetic code in daughter cells.

DNA polymerases are the primary enzymes responsible for DNA synthesis. Prokaryotes such as *Escherichia coli* have 3 major types of DNA polymerase: I, II, and III. All 3 **prokaryotic DNA polymerases** are capable of removing mismatched nucleotides via their **3' to 5' exonuclease ("proofreading") activity**. Only **DNA polymerase I** has **5' to 3' exonuclease activity**, which is used to remove the RNA primer synthesized by RNA primase **(Choice D)**.

(Choice A) In prokaryotes, topoisomerase II (DNA gyrase) temporarily cleaves both strands of the DNA double helix and introduces negative supercoils into the circular DNA to relieve tension created during strand unwinding.

(Choice B) One of the major methods of DNA damage by ultraviolet (UV) light is the dimerization of adjacent pyrimidine bases to form thymidine dimers. These dimers are routinely formed after exposure to sunlight but are usually removed via nucleotide excision repair by the enzyme UV-specific endonuclease.

(Choice E) Helicase promotes unwinding and dissociation of parent DNA strands at the replication fork.

Educational objective:
All 3 prokaryotic DNA polymerases can remove mismatched nucleotides via their 3' to 5' exonuclease ("proofreading") activity. Only DNA polymerase I has 5' to 3' exonuclease activity, which is used to remove the RNA primer synthesized by RNA primase.

References

- DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.

Biochemistry	General Principles	Dna replication
Subject	System	Topic

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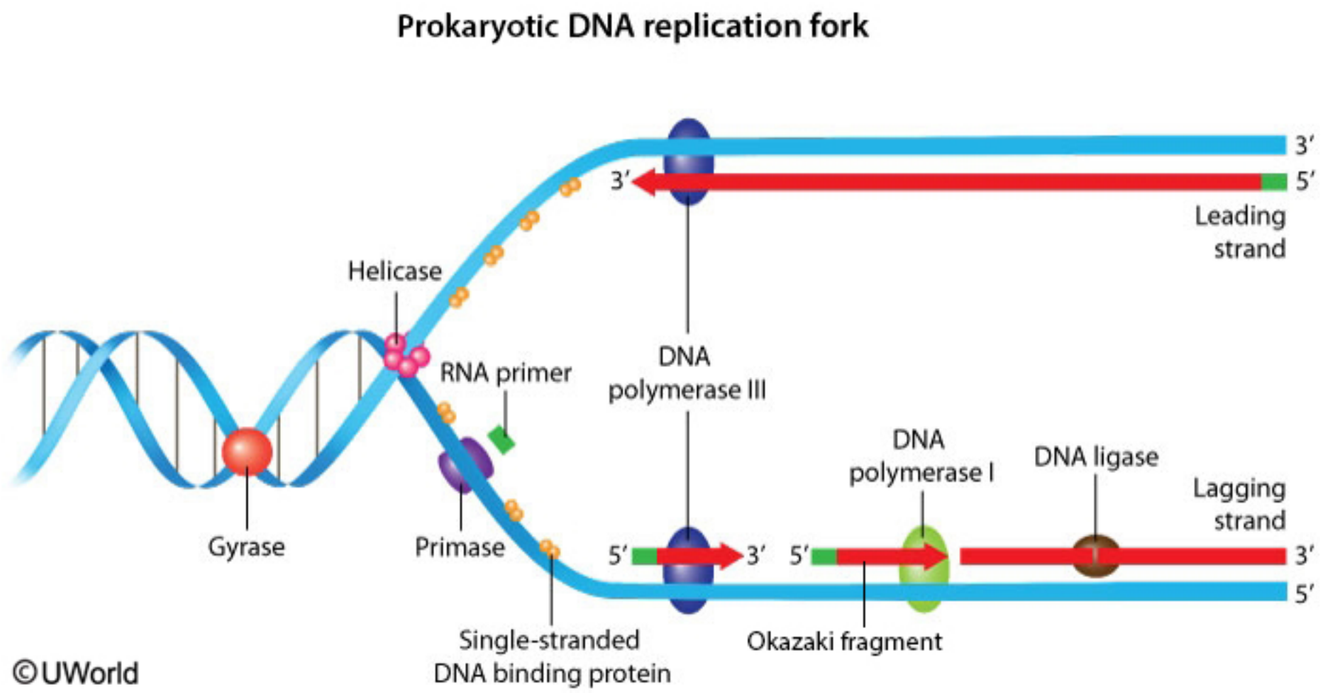

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A 12-year-old boy is brought to the emergency department with severe chest pain. He has had intermittent substernal chest pain for the past few months that typically occurs after heavy activity. The boy's activities have been limited due to the chest pain, and he is no longer able to play on the soccer team. The patient does not use tobacco or illicit drugs. His temperature is 36.7 C (98 F), blood pressure is 130/80 mm Hg, pulse is 132/min, respirations are 24/min, and pulse oximetry is 98% on room air. BMI is 17 kg/m^2. Physical examination shows an anxious-appearing boy with a rapid but regular pulse. No abnormalities are seen. Troponin is elevated, and ECG reveals ST segment elevations in leads II, III, and aVF. After acute stabilization and treatment, further laboratory workup shows an increased serum methionine level. Which of the following amino acids is most likely essential in this patient?

- A. Asparagine
- B. Cysteine
- C. Isoleucine
- D. Leucine
- E. Tyrosine
- F. Valine

Submit

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- A. Asparagine (4%)
- ✓ B. Cysteine (73%)
- C. Isoleucine (1%)
- D. Leucine (3%)
- E. Tyrosine (14%)
- F. Valine (2%)

Omitted
Correct answer
B

73%
Answered correctly

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Explanation

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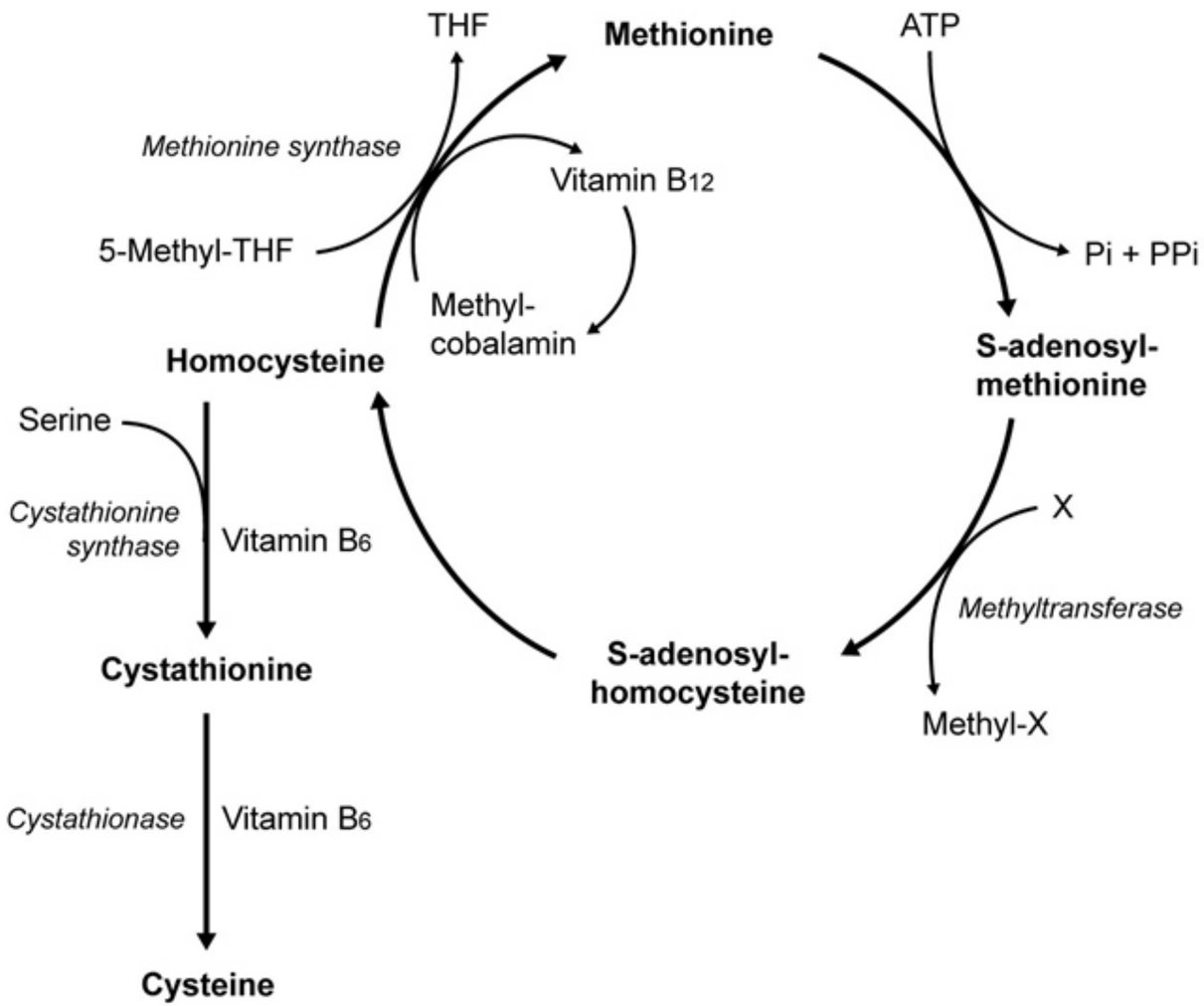
Methionine cycle



ATP = adenosine 5'-triphosphate; **Pi** = inorganic orthophosphate;

The amino acid methionine can be metabolized into S-adenosyl-methionine (SAM), which acts as a methyl-donor for many methyltransferase reactions. After the transfer of a methyl group, SAM is converted into S-adenosyl-homocysteine, which is broken down to form adenosine and homocysteine. Subsequently, the conversion of homocysteine to cystathionine requires the enzyme cystathionine synthase, the amino acid serine, and the cofactor vitamin B_6. Cystathionine is then converted to cysteine by the enzyme cystathionase, which also requires vitamin B_6 as a cofactor. Alternatively, the enzyme methionine synthase uses vitamin B_{12} as a cofactor to revert homocysteine back to methionine.

This patient most likely has **homocystinuria**, a condition that leads to **hypercoagulability** and **thromboembolic occlusion**. Because homocysteine is prothrombotic, individuals with complete cystathionine synthase deficiency can develop premature acute coronary syndrome, as seen in this patient (based on his troponin level and ECG findings). Other clinical features include **ectopia lentis** (ocular lens displacement) and **intellectual disability**.

The most common cause of homocystinuria is a defect in **cystathionine synthase**. Affected patients cannot form cysteine from homocysteine; therefore, cysteine is essential in their diet. In addition, homocysteine buildup results in **hypermethioninemia**, as seen in this patient.

(Choice A) The enzyme asparagine synthase converts aspartate to asparagine, the amino acid that is essential for rapidly dividing tumor cells that cannot produce it quickly enough on their own. The chemotherapy drug asparaginase decreases asparagine concentration in tumor cells and leads to lysis of these rapidly growing cells.

(Choices C, D, and F) Maple syrup urine disease is an amino acid disorder caused by deficiency of branched-chain α-ketoacid dehydrogenase. This deficiency leads to toxic buildup of branched-chain amino acids (leucine, isoleucine, and valine) and their metabolites, resulting in feeding difficulties, seizures, cerebral edema, and a sweet odor of the urine.

(Choice E) Phenylalanine hydroxylase catalyzes the hydroxylation of the essential amino acid phenylalanine to form tyrosine. Deficiency of phenylalanine hydroxylase is the most common cause of phenylketonuria, which results in severe intellectual disability if left untreated.

Educational objective:
Homocystinuria is most commonly caused by a defect in cystathionine synthase, resulting in an inability to form cysteine from homocysteine. Cysteine becomes essential in affected patients, and homocysteine buildup leads to elevated methionine. Homocysteine is prothrombotic, resulting in premature thromboembolic events (eg, atherosclerosis, acute coronary syndrome) in these patients.

References

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References

- Hypermethioninemias of genetic and non-genetic origin: A review.
- Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects.

Biochemistry	Gastrointestinal & Nutrition	Homocysteine
Subject	System	Topic

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A 54-year-old man with a history of cirrhosis is brought to the emergency department by his wife, who found him agitated and confused. She reports that he was nauseous and vomited bright red blood several times yesterday. His cirrhosis is secondary to chronic hepatitis C infection, and he has received treatment for esophageal varices in the past. Physical examination reveals abdominal distension, decreased liver span, and testicular atrophy. A jerky, irregular flexion-extension tremor involving his hands is seen with wrist extension. Which of the following is most likely to be elevated in this patient's astrocytes?

A. α-ketoglutarate
B. Alanine
C. Aspartate
D. Carbamoyl phosphate
E. Glutamine

Submit

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- A. α-ketoglutarate (17%)
- B. Alanine (13%)
- C. Aspartate (10%)
- D. Carbamoyl phosphate (14%)
- ✓ E. Glutamine (44%)

Omitted
Correct answer
E

44%
Answered correctly

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Time Spent

04/20/2020
Last Updated

Explanation

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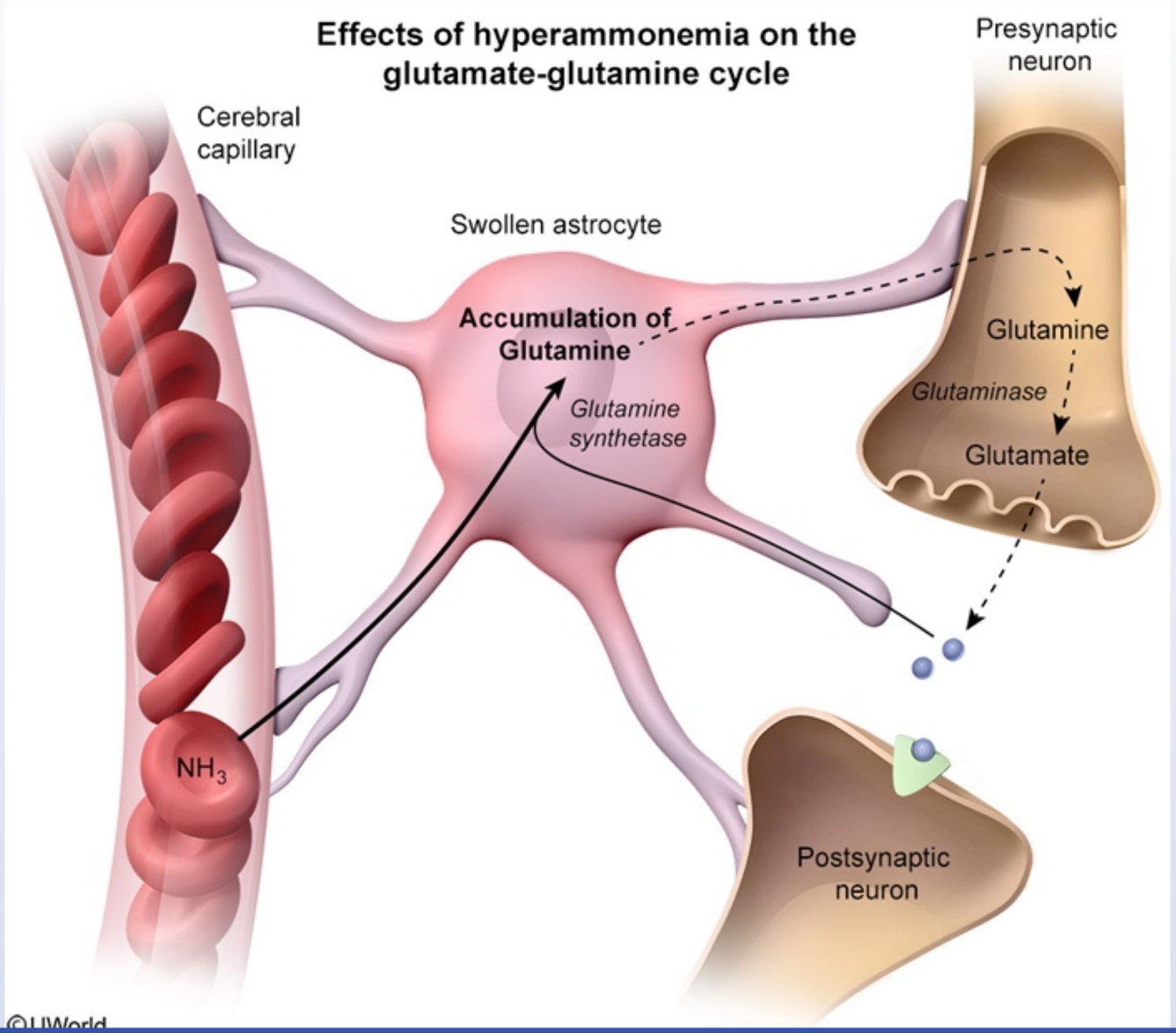

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This patient has hepatic encephalopathy, likely due to his recent gastrointestinal bleeding causing a corresponding increase in nitrogen absorption by the gut. The pathogenesis of hepatic encephalopathy is related to increased circulatory levels of **ammonia** and other neurotoxins due to failure of the liver to metabolize waste products.

Under normal conditions, astrocytes regulate neurotransmission by taking up glutamate present in the synapse, preventing excessive neuronal excitation. Through the action of glutamine synthetase, glutamate undergoes a condensation reaction with ammonia to form glutamine (a non-neuroactive compound). Glutamine is then released by the astrocytes and taken up by neurons, where it is converted back to glutamate for use as a neurotransmitter (glutamate-glutamine cycle).

When **excess ammonia** is present in the blood, it crosses the blood-brain barrier and is taken up by astrocytes, **increasing glutamine production**. The presence of excess glutamine within astrocytes leads to increased intracellular osmolarity, causing astrocyte swelling and impaired glutamine release. Hyperammonemia consequently decreases the amount of glutamine available for conversion to glutamate in neurons, resulting in **disruption of excitatory neurotransmission**.

(Choice A) α-ketoglutarate functions as a key intermediate in the TCA cycle and as a nitrogen transporter in metabolic reactions. In the setting of hyperammonemia, ammonia is detoxified to glutamate via glutamate dehydrogenase, depleting α-ketoglutarate and impairing energy metabolism in the brain.

(Choice B) Alanine is an amino group transporter in the glucose-alanine cycle in liver and muscle tissue. This process allows tissues that use amino acids for fuel to shunt excess nitrogen back to the liver.

(Choice C) Aspartate is a nonessential amino acid that functions as a substrate in the urea cycle and as part of the malate-aspartate shuttle that transfers cytosolic-reducing equivalents into the mitochondrial matrix.

(Choice D) Carbamoyl phosphate is a urea cycle intermediate synthesized by carbamoyl phosphate synthetase I, which transfers an ammonia molecule from glutamine or glutamate to a phosphorylated bicarbonate. Carbamoyl phosphate production is decreased in patients with advanced liver disease.

Educational objective:

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Educational objective:
Hyperammonemia in advanced liver failure occurs as a direct result of the cirrhotic liver's inability to metabolize nitrogenous waste products. Ammonia crosses the blood-brain barrier and causes excess glutamine to accumulate within astrocytes. This decreases the amount of glutamine available for conversion to glutamate in the neurons, resulting in disruption of excitatory neurotransmission.

References

- Ammonium metabolism in humans.
- Roles of glutamine in neurotransmission.
- The role of glutamine synthetase and glutamate dehydrogenase in cerebral ammonia homeostasis.

Biochemistry	Gastrointestinal & Nutrition	Hepatic Encephalopathy
Subject	System	Topic

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(Choice C) Aspartate is a hat
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Educational objective:

Exhibit Display

Hepatic encephalopathy	
Precipitating factors	• Drugs (eg, sedatives, narcotics) • Hypovolemia (eg, diarrhea) • Electrolyte changes (eg, hypokalemia) • ↑ Nitrogen load (eg, GI bleeding) • Infection (eg, pneumonia, UTI, SBP) • Portosystemic shunting (eg, TIPS)
Clinical presentation	• Sleep pattern changes • Altered mental status • Ataxia • Asterixis
Treatment	• Correct precipitating causes (eg, fluids, antibiotics) • ↓ Blood ammonia concentration (eg, lactulose, rifaximin)

GI = gastrointestinal; SBP = spontaneous bacterial peritonitis; TIPS = transjugular intrahepatic portosystemic shunt; UTI = urinary tract infection.

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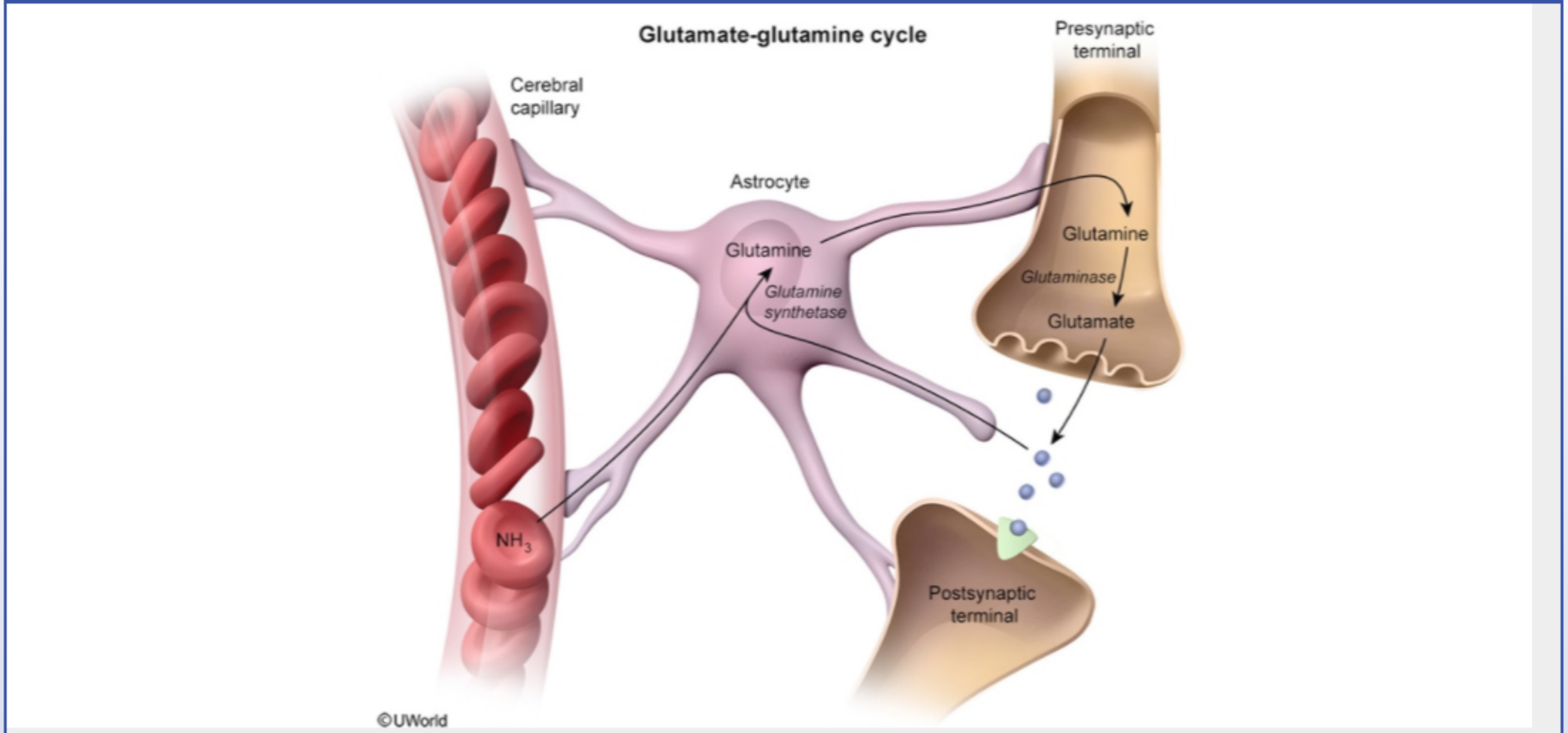

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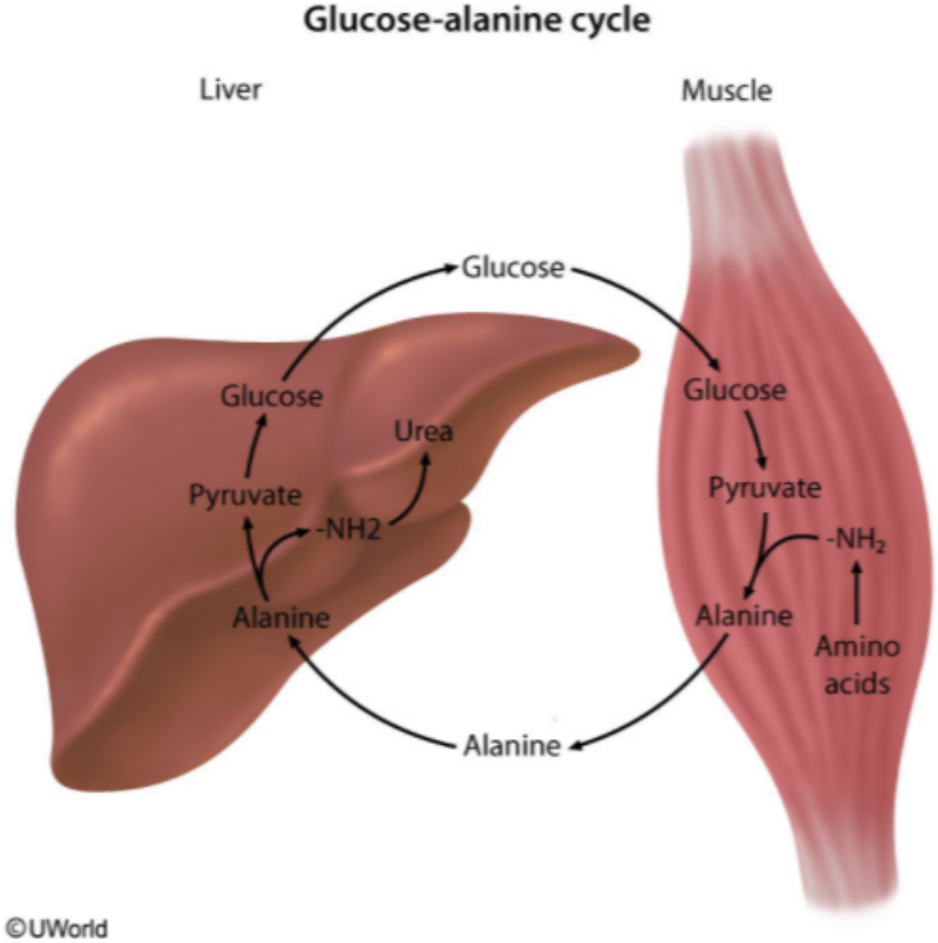
Educational objective:

Under normal conditions, astrocytes regulate neurotransmission by taking up glutamate present in the synapse, preventing excessive neuronal

Exhibit Display



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- Ammonium metabolism in humans

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Biochemistry	Gastrointestinal & Nutrition	Hepatic Encephalopathy
Subject	System	Topic

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A 47-year-old homeless man comes to the emergency department due to a "pins-and-needles" sensation in his legs. He also has painful lesions on his lips and corners of his mouth. He has had no loss of consciousness, nausea, vomiting, or diplopia. The patient drinks alcohol heavily on a daily basis and has a history of intravenous heroin use. On physical examination, he appears unkempt and ill appearing. Temperature is 36.8 C (98.2 F), blood pressure is 146/90 mm Hg, and pulse is 106/min. He has glossitis and angular stomatitis. Abdominal examination reveals hepatomegaly. Laboratory evaluation shows very low urinary riboflavin excretion. Activity of which of the following enzymes is most likely directly impaired in this patient?

- A. Fumarase
- B. Glucose-6-phosphate dehydrogenase
- C. HMG-CoA reductase
- D. Isocitrate dehydrogenase
- E. Malate dehydrogenase
- F. Succinate dehydrogenase
- G. Succinate thiokinase

Submit

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- A. Fumarase (7%)
- B. Glucose-6-phosphate dehydrogenase (7%)
- C. HMG-CoA reductase (6%)
- D. Isocitrate dehydrogenase (14%)
- E. Malate dehydrogenase (9%)
- ✓ F. Succinate dehydrogenase (50%)
- G. Succinate thiokinase (4%)

Omitted
Correct answer
F

50%
Answered correctly

03 secs
Time Spent

01/20/2020
Last Updated

Explanation

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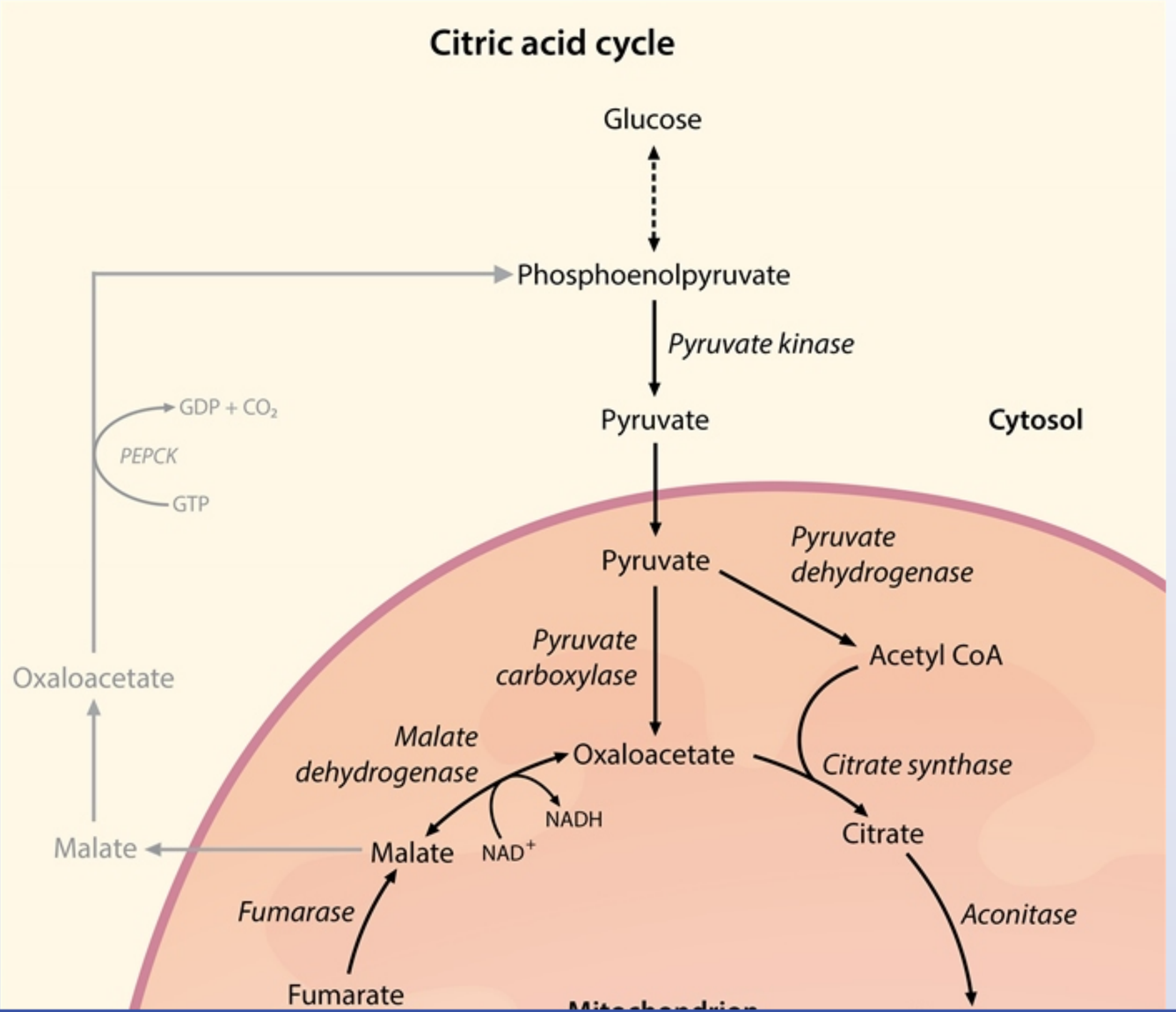

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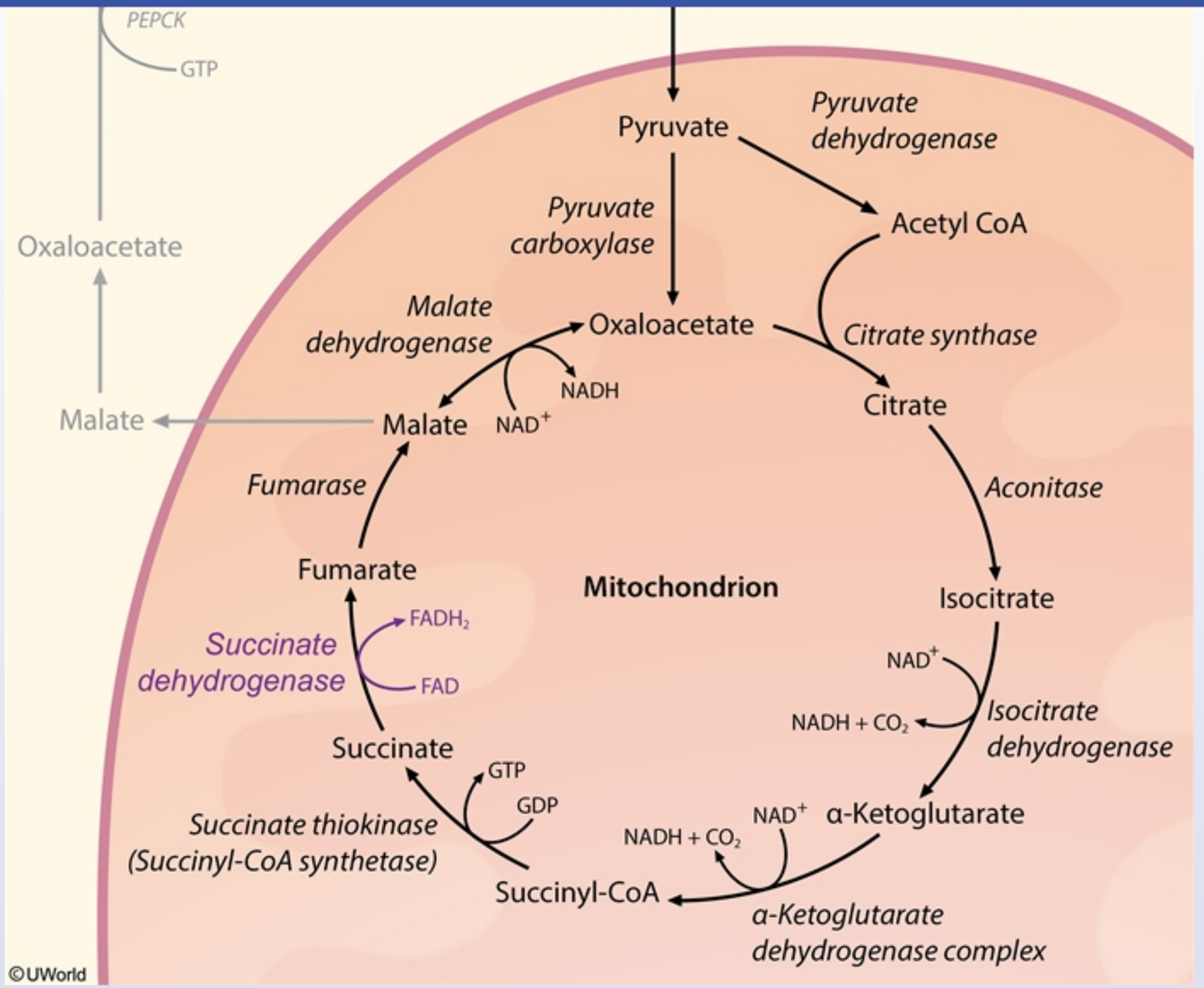

This patient's low urinary riboflavin excretion suggests a significant deficiency in riboflavin intake. Symptomatic **riboflavin deficiency** is rare in the United States but can be seen in chronic alcoholics and the severely malnourished. Clinical manifestations include angular stomatitis, cheilitis

©UWorld

This patient's low urinary riboflavin excretion suggests a significant deficiency in riboflavin intake. Symptomatic **riboflavin deficiency** is rare in the United States but can be seen in chronic alcoholics and the severely malnourished. Clinical manifestations include angular stomatitis, cheilitis, glossitis, seborrheic dermatitis, eye changes (eg, keratitis, corneal neovascularization), and anemia.

The **riboflavin** (vitamin B_2)-containing coenzymes are key constituents of the **electron transport chain**. Typically, riboflavin is first phosphorylated to become flavin mononucleotide (FMN), which can then be integrated into a coenzyme-flavin complex or further phosphorylated to flavin adenine dinucleotide (FAD). FMN and FAD participate as coenzymes in numerous reduction-oxidation reactions and are converted into reduced, energy-carrying states ($FMNH_2$ and $FADH_2$) through the acceptance of electrons.

FMN serves as a component of complex I, whereas FAD functions as a component of **succinate dehydrogenase** (complex II). Complex II participates in both the electron transport chain and tricarboxylic acid (TCA) cycle. During the TCA cycle, succinate dehydrogenase converts succinate to fumarate and transfers electrons to coenzyme Q (ubiquinone) via FAD. Complex II also accepts electrons from other sources of $FADH_2$, such as fatty acid oxidation.

(Choices A, D, E, and G) Isocitrate dehydrogenase, succinate thiokinase, malate dehydrogenase, and fumarase are enzymes that participate in the TCA cycle but do not use FAD or FMN as cofactors.

(Choice B) Reduced glutathione is an antioxidant that minimizes oxidative damage in many cells. Glutathione reductase regenerates reduced glutathione using nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor and FAD as a cofactor. Although glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the pentose phosphate pathway and supplies the necessary NADPH, it does not use FAD as a cofactor.

(Choice C) HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway. FMN and FAD are not used as cofactors.

Educational objective:
Riboflavin is a precursor of the coenzymes FMN and FAD. FAD participates in the tricarboxylic acid cycle and electron transport chain by acting as an electron acceptor for succinate dehydrogenase (complex II), which converts succinate into fumarate.

References

- Update on clinical aspects and treatment of selected vitamin-responsive disorders II (riboflavin and CoQ 10).

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References

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Biochemistry	Gastrointestinal & Nutrition	Tca cycle
Subject	System	Topic

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A researcher develops 2 functional mRNA sequences composed of CUC and CUU trinucleotide repeats, respectively. He subsequently incubates these mRNAs in a solution containing functional ribosomes and tRNAs charged with the appropriate amino acids. After several hours, it is found that both mRNA sequences produce polypeptide chains containing leucine repeats. This observed finding is due to which of the following genetic principles?

A. Ambiguity
B. No punctuation
C. Transition
D. Universality
E. Wobble

Submit

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- A. Ambiguity (11%)
- B. No punctuation (0%)
- C. Transition (2%)
- D. Universality (7%)
- ✓ E. Wobble (78%)

Omitted
Correct answer
E

78%
Answered correctly

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Explanation

Wobble hypothesis

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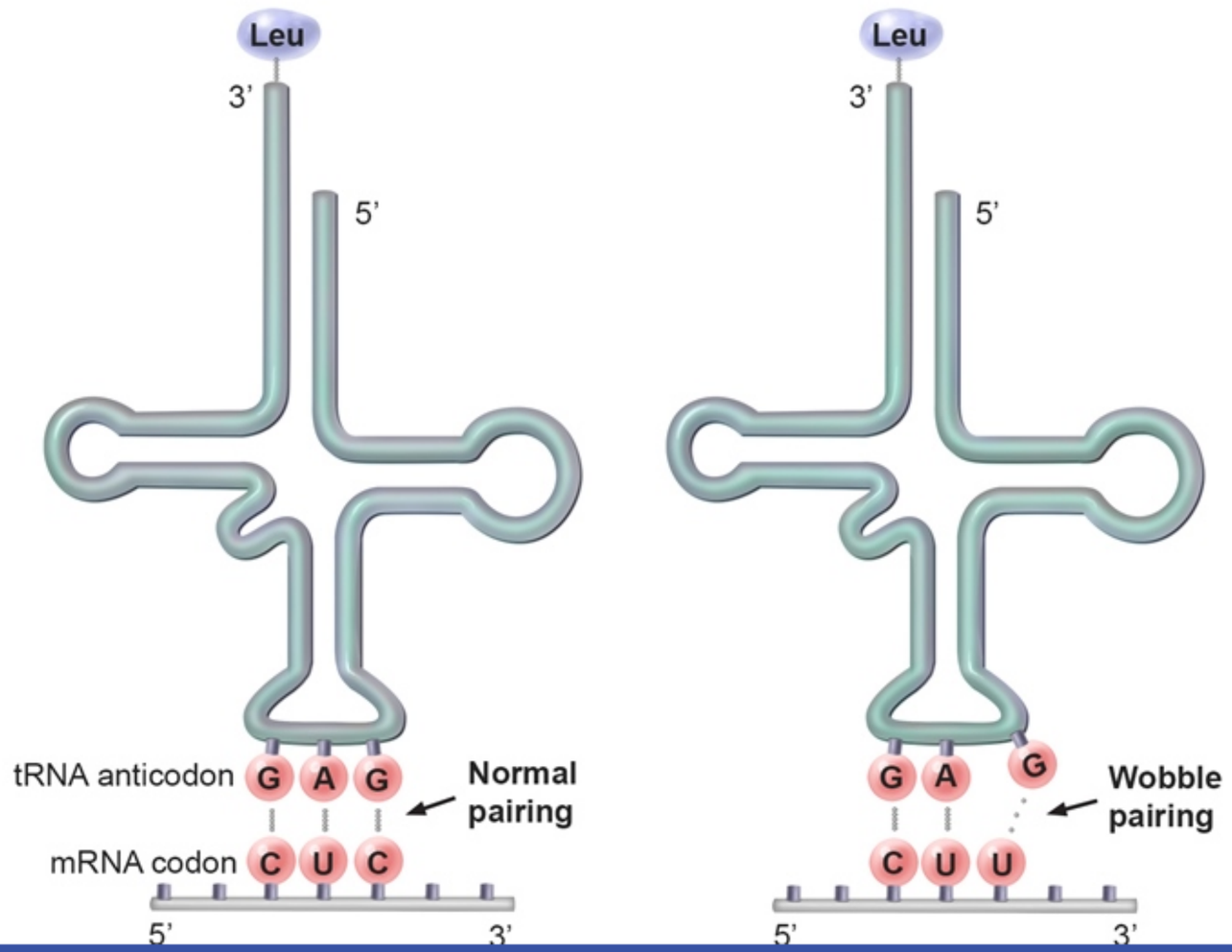
Wobble hypothesis



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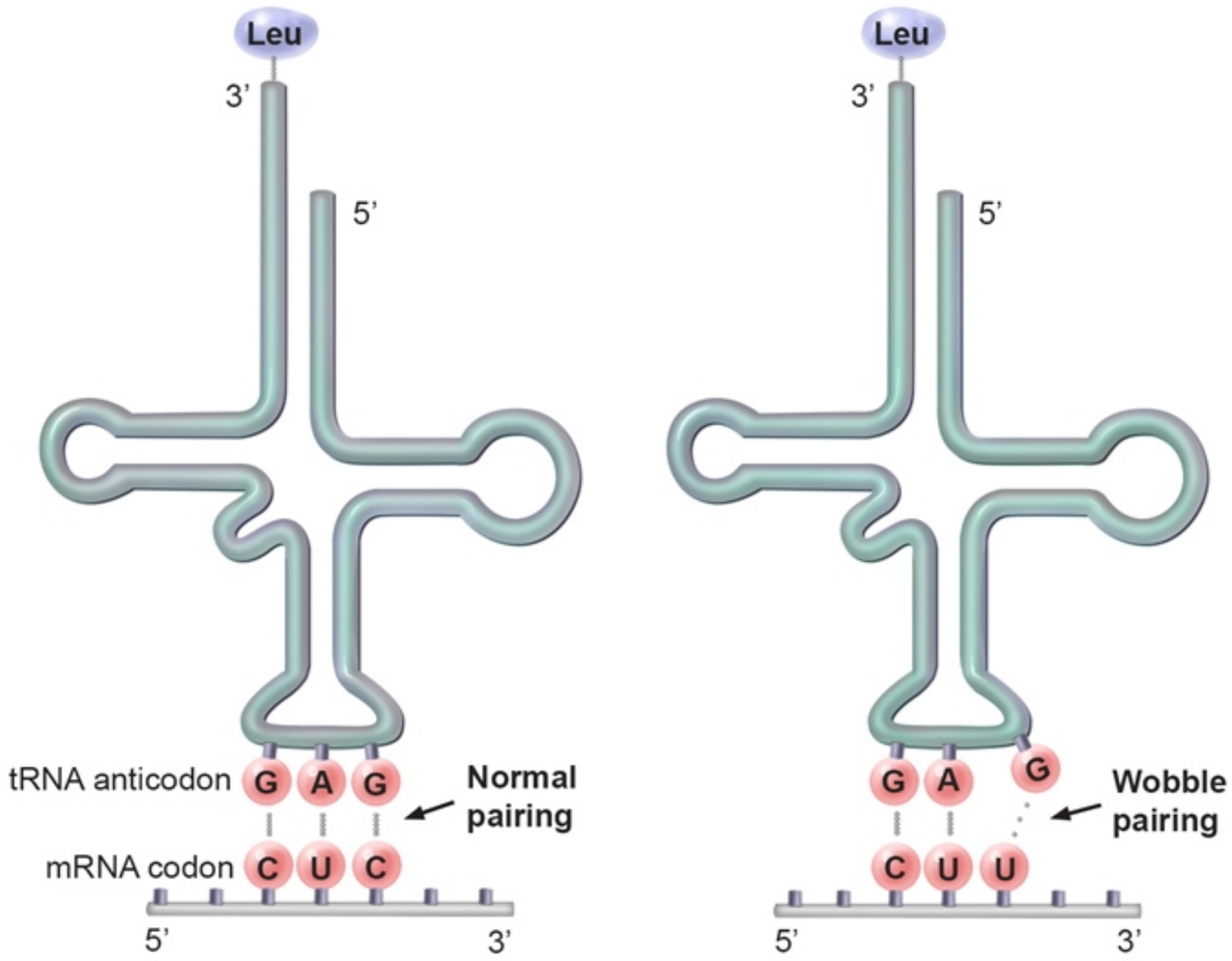
Wobble hypothesis



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There are 61 codons that code for amino acids, but only 20 amino acids are used in protein synthesis. The **genetic code** is therefore considered **"degenerate"** because more than 1 codon can code for a particular amino acid. For instance, the codons CUC and CUU both code for the amino acid leucine.

Individual tRNA molecules are specific for certain amino acids and recognize the mRNA codons associated with those amino acids. Certain tRNA molecules can recognize **multiple different codons** coding for the **same amino acid**, a phenomenon explained by the **wobble hypothesis**. This hypothesis states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing with their complementary nucleotides on tRNA, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing. In the case of leucine, for example, 1 tRNA molecule recognizes 2 codons (CUC and CUU) because only the first 2 nucleotide positions (CU in the codon) form traditional bonds.

(Choice A) The genetic code is not ambiguous as each codon is associated with only a single amino acid.

(Choice B) The genetic code is read sequentially from a starting point and has no internal punctuation as each codon is adjacent to the next without spacer nucleotides in between.

(Choice C) Genetic transition refers to a point mutation that results in replacement of a purine nucleotide for another purine or a pyrimidine nucleotide for another pyrimidine. In contrast, transversion refers to a point mutation that results in the replacement of a purine nucleotide for a pyrimidine or a pyrimidine nucleotide for a purine.

(Choice D) The genetic code is almost universal as amino acid codons are nearly identical across species; however, mitochondria and some bacteria and single-celled eukaryotes deviate from the standard genetic code.

Educational objective:
The genetic code is considered "degenerate" because more than 1 codon can code for a particular amino acid. Some of this degeneracy is explained by the wobble hypothesis, which states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing.

References

- tRNA's wobble decoding of the genome: 40 years of modification

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References

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Biochemistry	General Principles	Rna structure & function
Subject	System	Topic

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Molecular biologists undertake a series of experiments designed to classify proteins involved in various intracellular signaling pathways. During one of the experiments, a protein mixture obtained from a cell culture is separated by gel electrophoresis and subsequently transferred to a filter membrane. Labeled double-stranded DNA probes are then used to detect a specific protein of interest in the sample. Which of the following proteins is most likely to be detected by this method?

A. Ras

B. c-Jun

C. β1-adrenoreceptor

D. S-100

E. Adenylate cyclase

Submit

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- A. Ras (35%)
- ✓ B. c-Jun (27%)
- C. β1-adrenoreceptor (3%)
- D. S-100 (13%)
- E. Adenylate cyclase (19%)

Omitted
Correct answer
B

27%
Answered correctly

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Time Spent

03/03/2020
Last Updated

Explanation

Blotting technique	Substance detected	Type of probe
Northern	RNA	Single-stranded DNA or RNA (hybridization probe)
Southern	DNA	

Blotting technique	Substance detected	Type of probe
Northern	RNA	Single-stranded DNA or RNA (hybridization probe)
Southern	DNA	
Western	Protein	Antibody
Southwestern	DNA-binding protein	Double-stranded DNA

The Southern, Western, Northern, and Southwestern blot procedures are powerful techniques used to analyze and identify DNA fragments, proteins, mRNA, and DNA-bound proteins, respectively. The same basic technique underlies all of the blot procedures. First, the unknown sample is separated by gel electrophoresis. Separation occurs based on a molecule's size and charge. The separated molecules form bands on the gel that are then blotted onto a nitrocellulose membrane and incubated with a labeled probe to identify the specific DNA fragment, RNA molecule, or protein of interest.

Southwestern blots are used to identify and isolate proteins that bind DNA. In this technique, the target protein binds to a labeled, double-stranded DNA probe that is homologous to the protein's regulatory sequence. Of the molecules listed, c-Jun is the only DNA-binding protein. c-Jun and c-Fos are nuclear transcription factors that directly bind DNA via a leucine zipper motif. The genes that code for c-Jun and c-Fos are proto-oncogenes, genes that can become oncogenes following a mutation or with constitutive expression.

(Choice A) Ras is a proto-oncogene that codes for a membrane-bound G-protein. This G-protein acts as a secondary mediator for several hormones and cytokines that act on cell membrane receptors. Ras activation activates the MAP kinase pathway and ultimately affects transcription. However, Ras itself does not bind directly to DNA.

(Choices C and E) The β1-adrenergic receptor is a classic Gs-protein-coupled receptor located in the cell membrane. It does not interact directly with DNA. Adenylyl cyclase is the enzyme that cleaves ATP to form cAMP, the second messenger associated with G_s-protein-coupled receptors.

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(Choice D) S-100 proteins are homodimeric calcium-binding proteins, similar in structure to calmodulin and important in intracellular functions such as protein phosphorylation and cell growth and differentiation. S-100 is a marker for cells of neural crest derivation (melanocytes and Schwann cells), as well as Langerhans cells and other dendritic cells.

Educational objective:
Southwestern blotting is used to detect DNA-binding proteins such as transcription factors, nucleases, and histones.

References

- Southwestern blotting in investigating transcriptional regulation.

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Biochemistry	General Principles	Dna structure & function
Subject	System	Topic

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A 46-year-old obese man is referred to a dietitian for evaluation of his food intake. He has been trying to lose weight but has been unsuccessful. The patient is 172.7 cm (5 ft 8 in) tall and weighs 113 kg (250 lb). Analysis of his food intake shows that he is consuming 3600 Calories a day. The dietitian recommends increasing physical activity and implementing a dietary plan. In the first phase, the patient is advised to reduce his daily dietary intake to 3,000 Calories, with 30% coming from protein. How much protein per day will this patient consume on the new dietary plan?

A. 130 g
B. 160 g
C. 180 g
D. 225 g
E. 250 g

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A 46-year-old obese man is referred to a dietitian for evaluation of his food intake. He has been trying to lose weight but has been unsuccessful. The patient is 172.7 cm (5 ft 8 in) tall and weighs 113 kg (250 lb). Analysis of his food intake shows that he is consuming 3600 Calories a day. The dietitian recommends increasing physical activity and implementing a dietary plan. In the first phase, the patient is advised to reduce his daily dietary intake to 3,000 Calories, with 30% coming from protein. How much protein per day will this patient consume on the new dietary plan?

A. 130 g (8%)
B. 160 g (6%)
C. 180 g (17%)
✓ D. 225 g (58%)
E. 250 g (8%)

Omitted
Correct answer
D

58%
Answered correctly

02 secs
Time Spent

03/16/2020
Last Updated

Explanation

Dietary energy comes predominantly from protein, carbohydrate, and fat. Metabolism yields 4 Calories (Cal) per gram of protein or carbohydrate and 9 Cal per gram of fat. Ethanol yields 7 Cal per gram.

This patient is instructed to consume 3000 Cal per day, 900 (30%) of which are to be from protein. Because 1 g of protein yields 4 Cal of energy, this patient should consume (900 Cal /4 Cal) = 225 g/day of protein.

Educational objective:

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B. 160 g (6%)

C. 180 g (17%)

✓ D. 225 g (58%)

E. 250 g (8%)

Omitted
Correct answer
D

58%
Answered correctly

02 secs
Time Spent

03/16/2020
Last Updated

Explanation

Dietary energy comes predominantly from protein, carbohydrate, and fat. Metabolism yields 4 Calories (Cal) per gram of protein or carbohydrate and 9 Cal per gram of fat. Ethanol yields 7 Cal per gram.

This patient is instructed to consume 3000 Cal per day, 900 (30%) of which are to be from protein. Because 1 g of protein yields 4 Cal of energy, this patient should consume (900 Cal /4 Cal) = 225 g/day of protein.

Educational objective:
Metabolism of 1 g of protein or carbohydrate produces 4 Calories of energy; metabolism of 1 g of fat produces 9 Calories.

Biochemistry	Gastrointestinal & Nutrition	Obesity
Subject	System	Topic

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Biochemistry researchers are investigating the speed at which various carbohydrates are metabolized within the liver. They hypothesize that different monosaccharides delivered to the liver have different rates of intracellular metabolism. Which of the following substances is most likely to have the fastest rate of metabolism in the glycolytic pathway?

A. Fructose-1-phosphate

B. Galactose-1-phosphate

C. Glucose-1-phosphate

D. Glucose-6-phosphate

E. Mannose-6-phosphate

Submit

Biochemistry researchers are investigating the speed at which various carbohydrates are metabolized within the liver. They hypothesize that different monosaccharides delivered to the liver have different rates of intracellular metabolism. Which of the following substances is most likely to have the fastest rate of metabolism in the glycolytic pathway?

- ✓ A. Fructose-1-phosphate (39%)
- B. Galactose-1-phosphate (1%)
- C. Glucose-1-phosphate (11%)
- D. Glucose-6-phosphate (45%)
- E. Mannose-6-phosphate (1%)

Omitted
Correct answer
A

39%
Answered correctly

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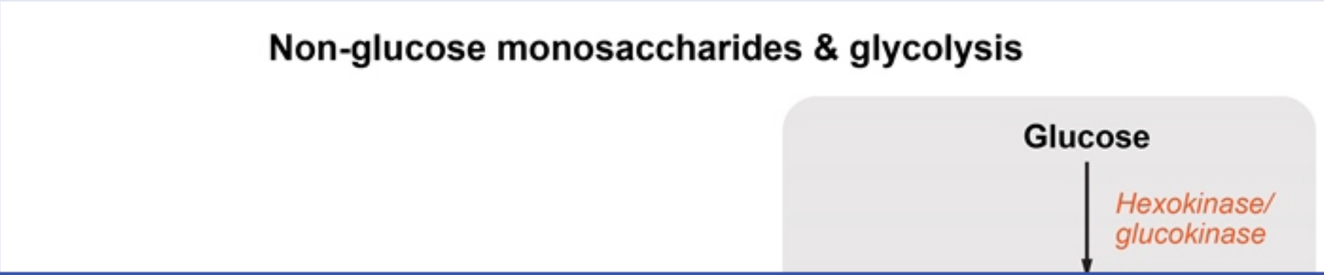
Time Spent

06/13/2020
Last Updated

Explanation



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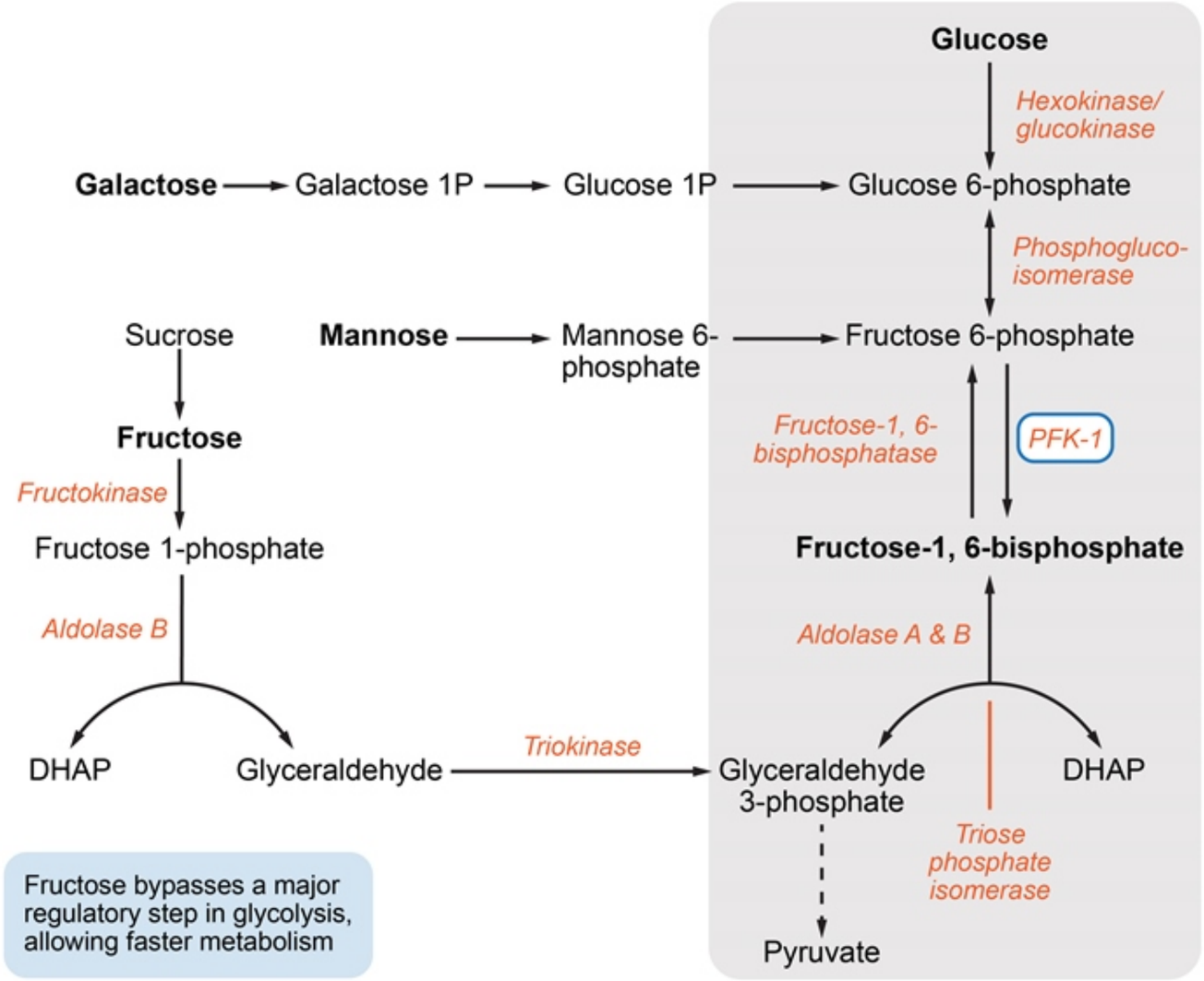
Non-glucose monosaccharides & glycolysis



Fructose bypasses a major regulatory step in glycolysis, allowing faster metabolism

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Non-glucose monosaccharides (eg, galactose, mannose, fructose) enter the glycolytic pathway at different points as **intermediates of glycolysis**. Of these, **fructose** is the only one whose metabolites **bypass phosphofructokinase**, one of the key enzymes involved in regulating the rate of glycolysis. As a result, fructose is metabolized by the liver faster than the other monosaccharides and is rapidly cleared from the bloodstream following dietary absorption.

Metabolism of fructose in the liver begins with phosphorylation by fructokinase to **fructose-1-phosphate (F1P)**. Aldolase B can use both fructose-1,6-bisphosphate and F1P as substrates; it converts F1P into **dihydroxy acetone phosphate (DHAP)** and **glyceraldehyde**. Glyceraldehyde can be either phosphorylated to glyceraldehyde-3-phosphate by triokinase or converted to DHAP. DHAP is converted by triose phosphate isomerase to glyceraldehyde-3-phosphate, which continues down the glycolytic pathway.

(Choices B, C, D, and E) Galactose-1-phosphate, glucose-1-phosphate, glucose-6-phosphate, and mannose-6-phosphate enter glycolysis upstream of phosphofructokinase, a major rate-limiting enzyme of glycolysis. This slows down the rate of their metabolism relative to fructose and its metabolites (eg, F1P).

Educational objective:
Dietary fructose is phosphorylated in the liver to F1P and is rapidly metabolized because it bypasses PFK-1, the major rate-limiting enzyme of glycolysis. Other sugars (eg, glucose, galactose, mannose) enter glycolysis prior to PFK-1 and as a result are metabolized more slowly.

Biochemistry	Gastrointestinal & Nutrition	Glycolysis
Subject	System	Topic

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A 74-year-old woman comes to the emergency department due to 2 days of left leg pain and numbness. She has a history of atrial fibrillation and hypertension. Her left lower limb is pale and cold to palpation below the knee. Arterial Doppler ultrasound shows an occluding thrombus, and a left femoral embolectomy is performed. Post-procedure dorsalis pedis and posterior tibial pulses become palpable. Several hours later, the patient begins to experience severe left calf pain. On repeat examination, the left calf is swollen, tense, and tender, and the pain worsens with dorsiflexion of the left foot. The distal pulses are also absent. The physician suspects injury of the reperfused muscles in part due to overproduction of reactive oxygen species. Which of the following enzymes is most likely to help neutralize these toxic molecules?

- A. Cytochrome oxidase
- B. Cytochrome P450
- C. Myeloperoxidase
- D. NADPH oxidase
- E. Superoxide dismutase

Submit

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- A. Cytochrome oxidase (4%)
- B. Cytochrome P450 (3%)
- C. Myeloperoxidase (6%)
- D. NADPH oxidase (17%)
- ✓ E. Superoxide dismutase (67%)

Omitted
Correct answer
E

67%
Answered correctly

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Time Spent

03/05/2020
Last Updated

Explanation

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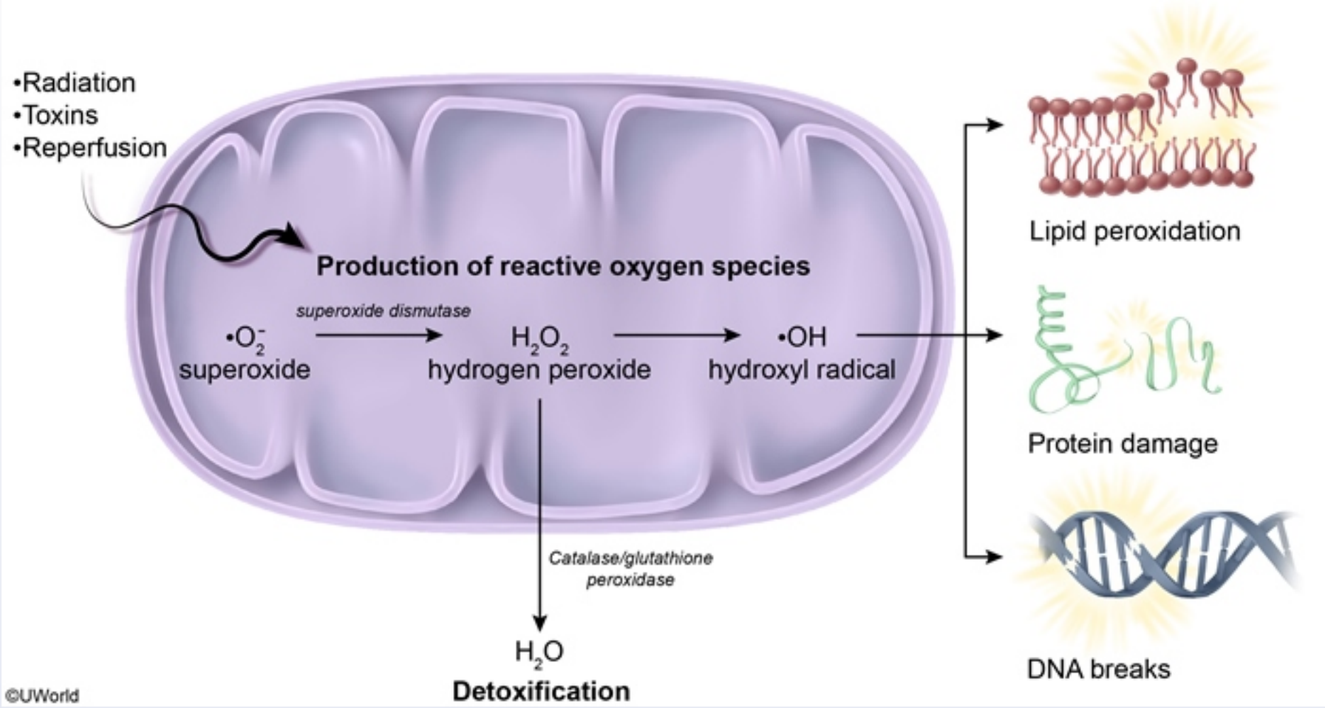

The vignette describes **acute compartment syndrome** secondary to reperfusion injury. Restoration of arterial blood flow to an affected limb floods ischemic tissue with oxygen. Molecular oxygen reacts with xanthine oxidase, NADPH oxidase, and nitric oxide synthase to form **reactive oxygen species (ROS)** such as superoxide, hydroxyl radicals, and singlet oxygen. ROS disrupt cellular functions leading to DNA mutations, protein synthesis disruption, and membrane lipid peroxidation.

Antioxidant enzymes, such as **superoxide dismutase, glutathione peroxidase**, **and catalase**, convert ROS to oxygen and water, neutralizing their capacity for cellular damage. ROS generated during cellular respiration are typically neutralized by antioxidants before they become problematic. However, in the **postischemic state**, the production of ROS exceeds the neutralizing capabilities of antioxidant enzymes (**high oxidative stress**), leading to increased cell injury and death.

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Antioxidant enzymes, such as **superoxide dismutase, glutathione peroxidase**, **and catalase**, convert ROS to oxygen and water, neutralizing their capacity for cellular damage. ROS generated during cellular respiration are typically neutralized by antioxidants before they become problematic. However, in the **postischemic state**, the production of ROS exceeds the neutralizing capabilities of antioxidant enzymes (**high oxidative stress**), leading to increased cell injury and death.

(Choice A) Cytochrome oxidase is the final component of the electron transport chain and functions to convert molecular oxygen to water while establishing the proton gradient necessary for synthesis of ATP.

(Choice B) Cytochrome P450 enzymes metabolize endogenous toxins as well as drugs. They are capable of producing reactive oxygen species, which can contribute to the hepatotoxicity seen with certain drugs.

(Choice C) Myeloperoxidase is found in neutrophils and converts hydrogen peroxide to hypochlorous acid, a bactericidal compound that also causes oxidative damage to host cells.

(Choice D) NADPH oxidase catalyzes the reduction of molecular oxygen to superoxide free radicals, aiding in bacterial destruction by phagocytic cells. Deficiency leads to chronic granulomatous disease in which those affected are unable to destroy catalase-positive organisms.

Educational objective:
As an antioxidant, superoxide dismutase neutralizes reactive oxygen species, preventing cell injury. In a pathologic state such as post-ischemic reperfusion, oxidative stress is high and reactive oxygen species production exceeds the neutralizing capability of antioxidants, leading to increased cell damage and death.

References

- Reperfusion injury and reactive oxygen species: The evolution of a concept.

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A 62-year-old man comes to the emergency department due to severe colicky upper abdominal pain, nausea, and vomiting. He reports several episodes of similar abdominal discomfort in the past. The patient does not use tobacco, alcohol, or illicit drugs. He immigrated to the United States from East Asia several years ago. Physical examination shows right upper quadrant abdominal tenderness. An imaging study shows several gallstones in the common bile duct and gallbladder. The stones are removed from the duct endoscopically, and a cholecystectomy is also performed. The gallstones are dark brown, soft, and composed primarily of calcium bilirubinate with variable amounts of cholesterol. Which of the following enzymes most likely played an important role in the pathogenesis of this patient's condition?

A. 7-alpha-hydroxylase

B. Aromatase

C. Beta-glucuronidase

D. Desmolase

E. HMG-CoA reductase

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- A. 7-alpha-hydroxylase (27%)
- B. Aromatase (1%)
- ✓ C. Beta-glucuronidase (45%)
- D. Desmolase (3%)
- E. HMG-CoA reductase (22%)

Omitted
Correct answer
C

45%
Answered correctly

02 secs
Time Spent

03/03/2020
Last Updated

Explanation

Pathogenesis of pigment stones

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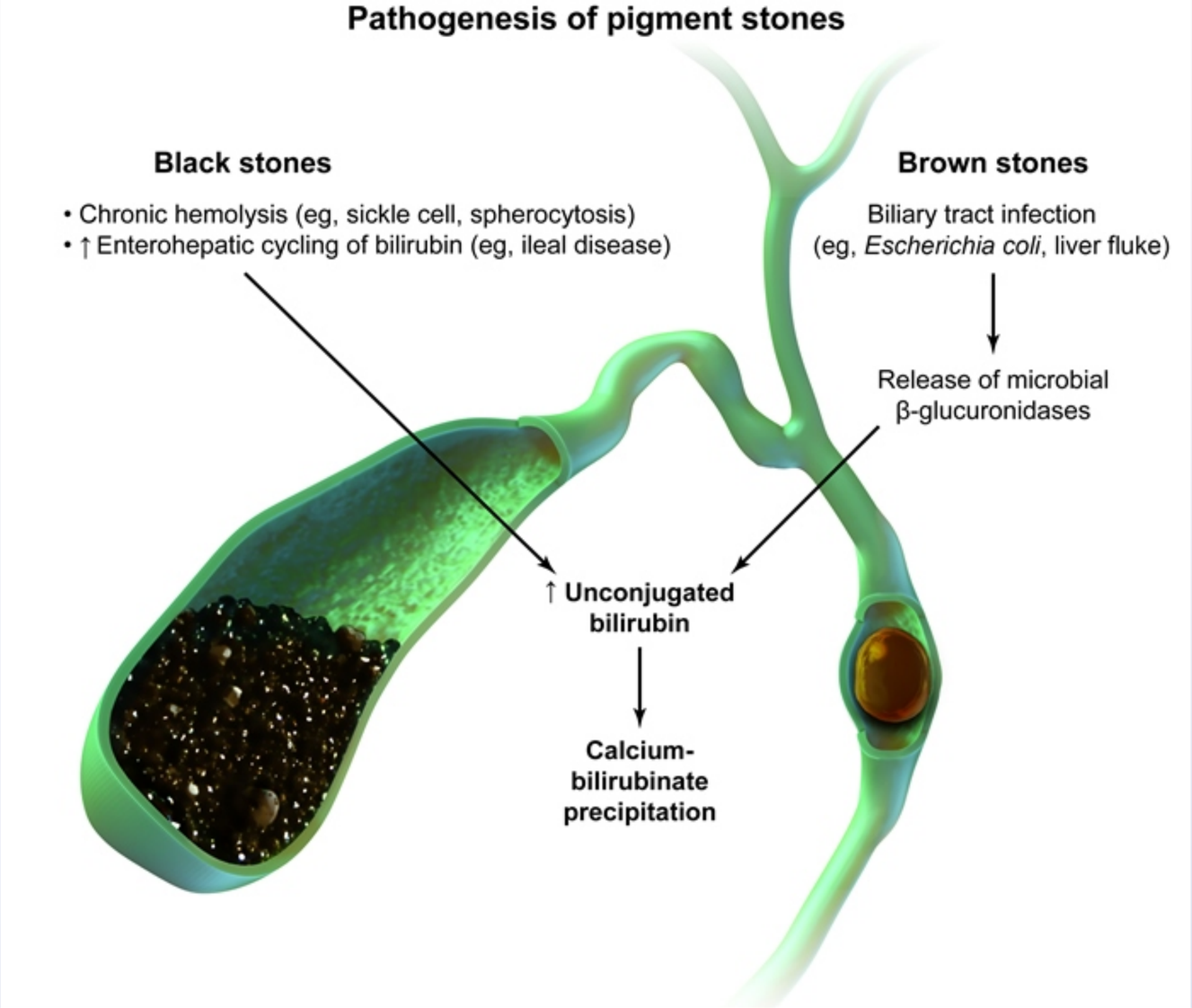

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Gallstones can be categorized as cholesterol, pigment, or mixed stones. Cholesterol stones are formed when the ability of bile salts to solubilize cholesterol is overwhelmed by high concentrations of cholesterol in bile. Cholesterol stones are yellow to pale gray and hard. By contrast, **pigment gallstones** are composed of calcium salts of **unconjugated bilirubin**, are comparatively soft, and are dark brown to black.

Brown pigment stones typically arise secondary to bacterial (eg, *Escherichia coli*) or helminthic (eg, *Ascaris lumbricoides, Clonorchis sinensis*) **infection of the biliary tract**, which results in the release of **beta-glucuronidase** by injured hepatocytes and bacteria. This enzyme hydrolyzes bilirubin glucuronides and increases the amount of unconjugated bilirubin. The liver fluke *C sinensis* is a common cause of pigmented stones in East Asian countries and can have a prolonged quiescent phase before inducing symptoms.

Pigment stones may also occur in the absence of infection when excess bilirubin is excreted, such as with chronic **hemolytic anemia**. A small amount of conjugated bilirubin normally becomes deconjugated by endogenous beta-glucuronidase in the biliary tract. When large amounts of conjugated bilirubin are excreted into the bile, enough becomes deconjugated to promote black pigment stone formation.

(Choice A) Inhibition of 7-alpha-hydroxylase (eg, fibrates) reduces the conversion of cholesterol to bile acids and increases the risk of cholesterol stones. However, this patient's gallstones are composed primarily of unconjugated bilirubin, not cholesterol.

(Choices B and E) Aromatase catalyzes the conversion of androgens to estrogen, which increases hepatic cholesterol uptake. In addition, estrogens upregulate HMG Co-A reductase, which increases cholesterol synthesis. This increases biliary excretion of cholesterol, favoring formation of cholesterol stones, not pigment stones.

(Choice D) Desmolase (cholesterol side-chain cleavage enzyme) catalyzes the conversion of cholesterol to pregnenolone, which is the first step in the synthesis of steroid hormones.

Educational objective:
Brown pigment gallstones are composed of calcium salts of unconjugated bilirubin and arise secondary to bacterial or helminthic infection of the biliary tract. Beta-glucuronidase released by injured hepatocytes and bacteria hydrolyzes bilirubin glucuronides to unconjugated bilirubin. The liver fluke *Clonorchis sinensis* has a high prevalence in East Asian countries and is a common cause of pigment stones.

References

- New pathophysiological concepts underlying pathogenesis of pigment gallstones.

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References

- New pathophysiological concepts underlying pathogenesis of pigment gallstones.
- Cholecystolithiasis is associated with Clonorchis sinensis infection.

Biochemistry	Gastrointestinal & Nutrition	Gallstone disease
Subject	System	Topic

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A 31-year-old man comes to the office for a routine checkup. He has no significant medical problems and does not take any medications. The patient works as a fitness trainer and lifts weights recreationally. He has been consuming carbohydrate-rich food prior to his weightlifting sessions and claims that it increases muscle strength. A literature review shows that the rate of glycogenolysis within myocytes increases several hundredfold during active skeletal muscle contraction. Which of the following substances is most likely responsible for increasing the reaction rate during active contraction?

A. ATP

B. Ca^{2+}

C. cAMP

D. Glucose-6-phosphate

E. Lactate

Submit

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- A. ATP (15%)
- ✓ B. Ca^{2+} (38%)
- C. cAMP (22%)
- D. Glucose-6-phosphate (6%)
- E. Lactate (16%)

Omitted
Correct answer
B

38%
Answered correctly

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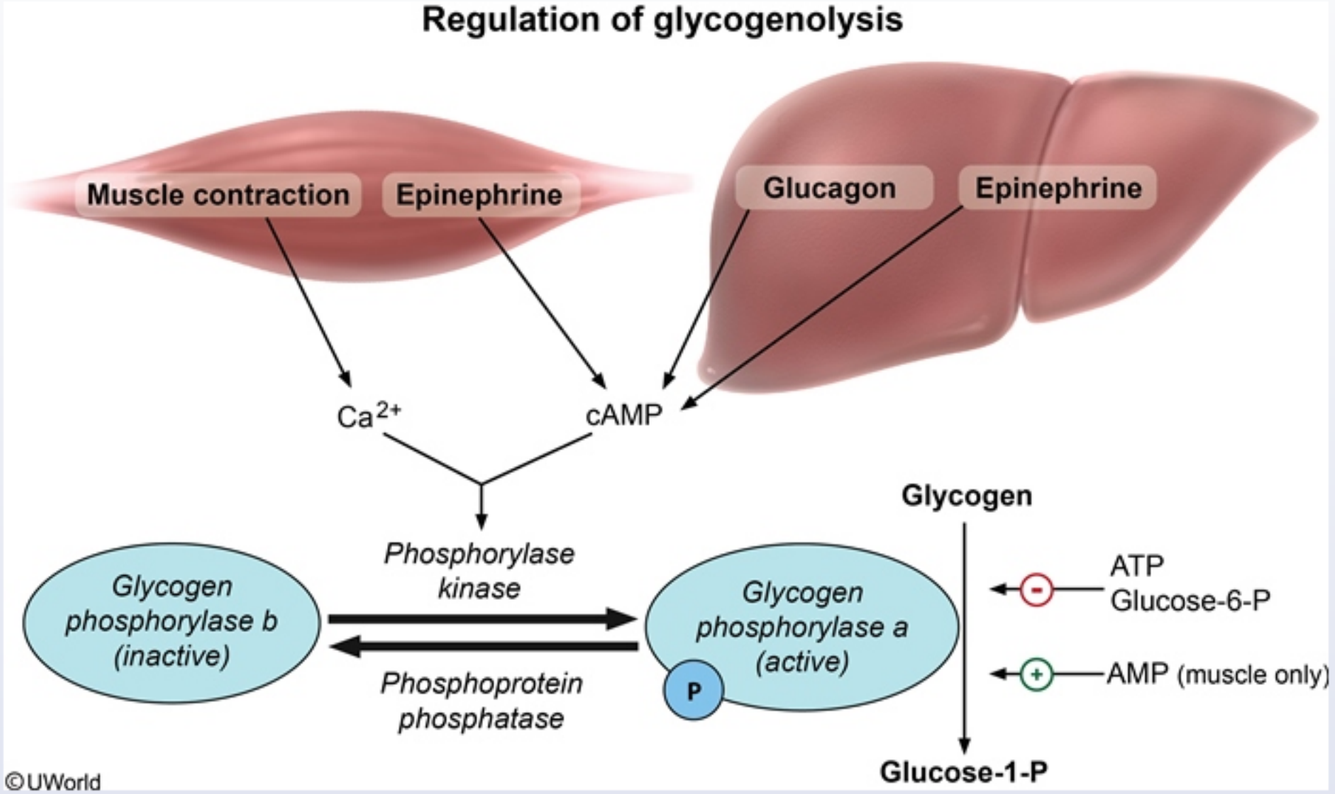
Time Spent

04/29/2020
Last Updated

Explanation

Explanation



Glycogen is broken down by the enzyme **glycogen phosphorylase**, which is regulated through phosphorylation (active state) and dephosphorylation (inactive state). **Phosphorylase kinase (PK)** is the enzyme responsible for the phosphorylation of glycogen phosphorylase, whereas **phosphoprotein phosphatase** catalyzes its dephosphorylation.

PK is regulated differently in liver than in muscles. Glycogen stored in the **liver** is used to maintain blood glucose levels during the fasting state, whereas glycogen in the muscles is used to provide energy for muscle contraction. In the liver, PK is activated primarily through the binding of **epinephrine and glucagon** to G_s protein-coupled receptors, which **increases cAMP concentrations** and causes phosphorylation of PK (via

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Glucose-1-P

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Skeletal muscle lacks glucagon receptors, but muscle PK can still be phosphorylated in response to an epinephrine-induced increase in cAMP concentrations. However, increased **intracellular calcium** is a more powerful activator of muscle PK. Release of sarcoplasmic calcium stores following neuromuscular acetylcholine stimulation allows for **synchronization** of skeletal muscle contraction and glycogen breakdown, providing the energy necessary for anaerobic muscle contraction.

(Choices A and D) Phosphorylated glycogen phosphorylase (active form) is allosterically inhibited by ATP and glucose-6-phosphate in both liver and muscle cells. Increased intracellular ATP levels help to decrease the rate of glycogenolysis upon cessation of active muscle contraction.

(Choice C) Although increased cAMP stimulates muscle glycogen breakdown via the action of epinephrine on beta-1 adrenergic receptors, it is not responsible for synchronization of active muscle contraction and glycogen breakdown.

(Choice E) Lactate is produced in tissues during anaerobic glycolysis, such as in muscles during strenuous exercise as a result of relatively hypoxic conditions. The lactate produced by the muscles can be converted to glucose in the liver via gluconeogenesis.

Educational objective:
Synchronization of glycogen degradation with skeletal muscle contraction occurs due to release of sarcoplasmic calcium following neuromuscular stimulation. Increased intracellular calcium causes activation of phosphorylase kinase, stimulating glycogen phosphorylase to increase glycogenolysis.

References

- Muscle glycogenolysis. Regulation of the cyclic interconversion of phosphorylase a and phosphorylase b

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References

- Muscle glycogenolysis. Regulation of the cyclic interconversion of phosphorylase a and phosphorylase b.

Biochemistry	General Principles	Physical exercise
Subject	System	Topic

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Microbiologists are investigating sugar metabolism in wild-type and mutant strains of *Escherichia coli*. Both strains are found to grow viable colonies on lactose-containing media. Each strain is then cultured on a new growth medium containing only glucose. Representative colonies of each strain from the new media undergo Western blot processing using a fluorescently labeled probe specific for β-galactosidase. Wild-type bacterial colonies are found to contain only trace quantities of β-galactosidase. However, the mutant colonies express significant amounts of β-galactosidase. Further analysis reveals that the variant strain contains a mutation that inhibits the binding of a certain protein to its regulatory sequence. In which of the following locations did this mutation most likely occur?

A. Activator protein (CAP) binding site

B. Operator locus

C. Promoter region

D. Activator protein (CAP) gene

E. RNA polymerase cistron

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A. Activator protein (CAP) binding site (19%)
✓ B. Operator locus (43%)
C. Promoter region (27%)
D. Activator protein (CAP) gene (8%)
E. RNA polymerase cistron (1%)

Omitted
Correct answer
B

43%
Answered correctly

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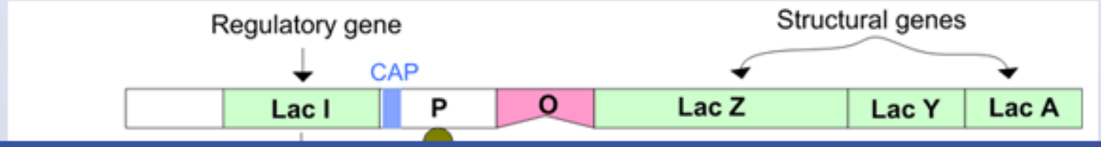
Time Spent

02/05/2020
Last Updated

Explanation



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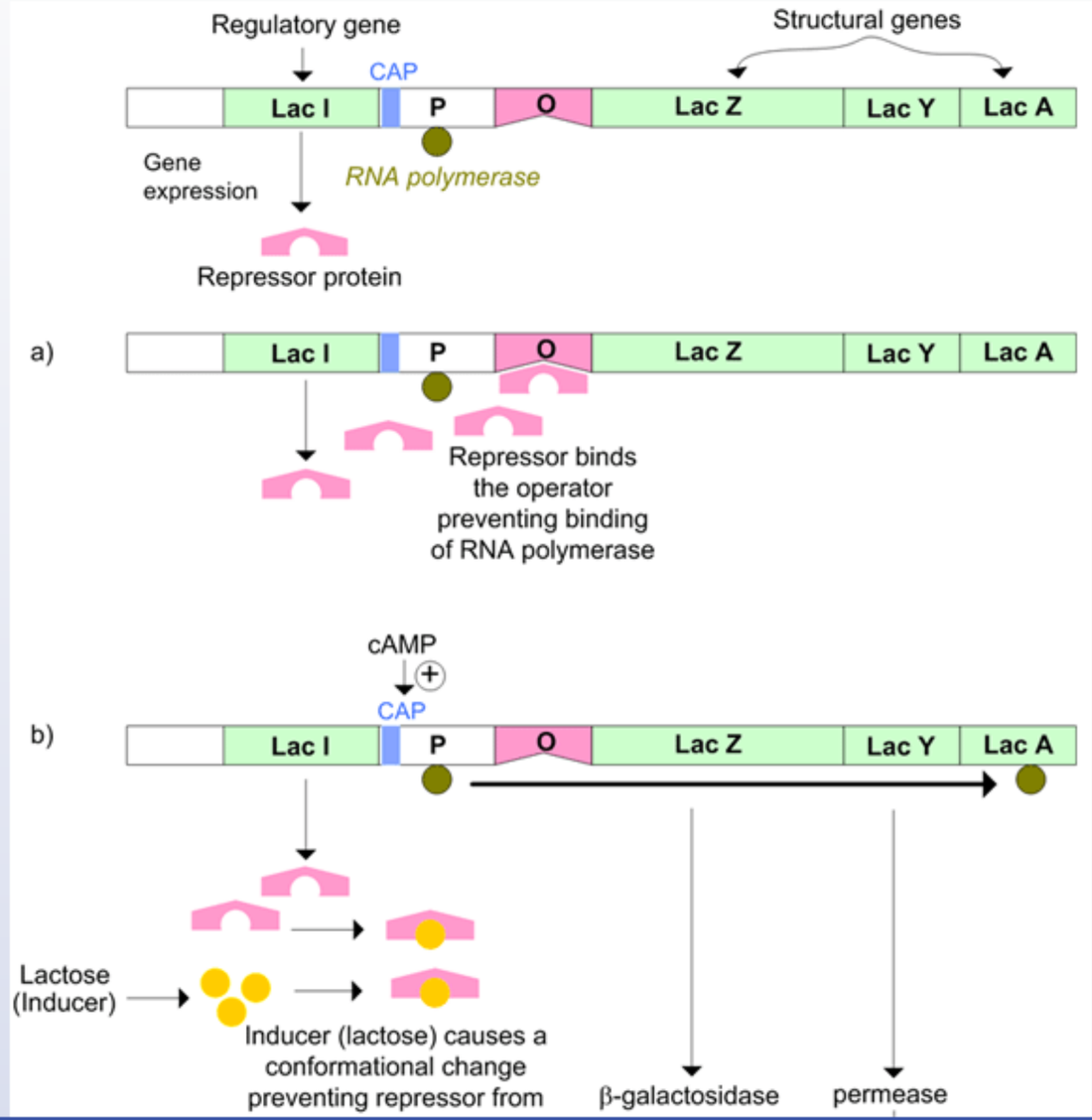

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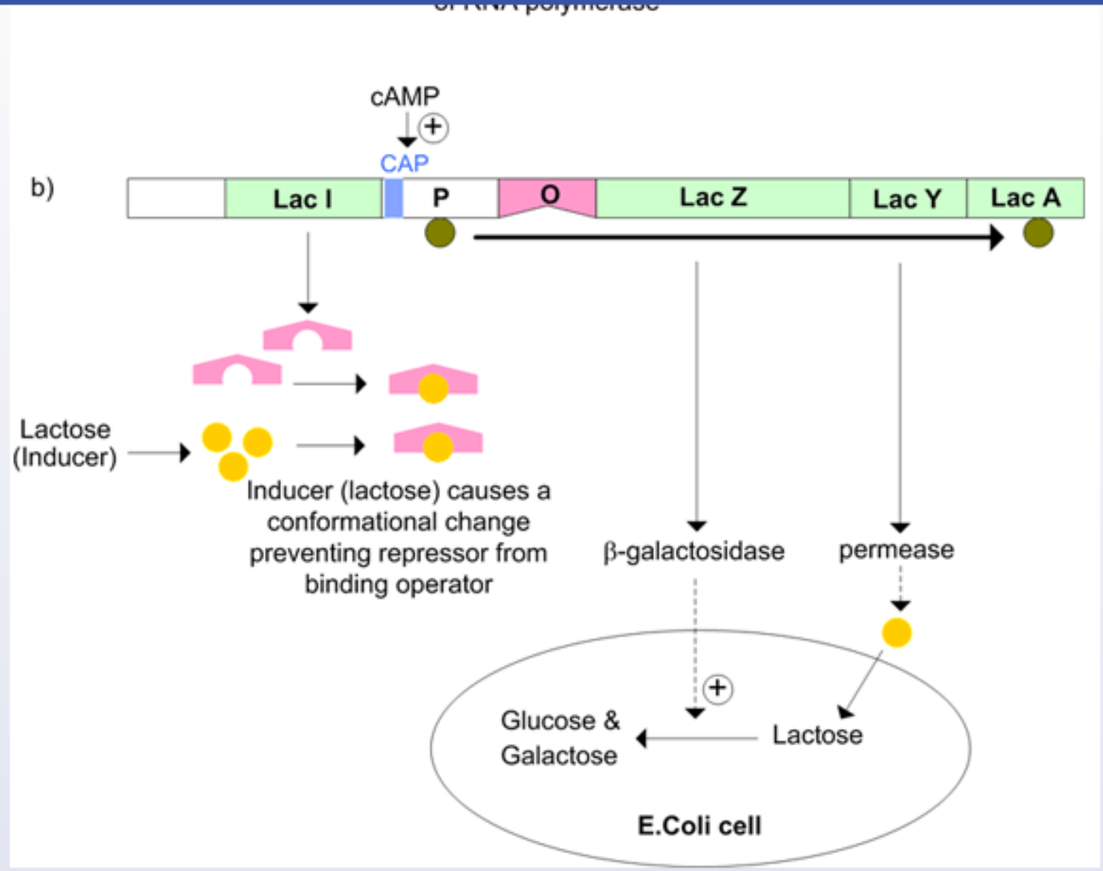

The *lac* operon consists of a regulatory gene (*lac I*), a promoter region (*lac p*), an operator region (*lac o*), and three structural genes (*lac Z, lac Y,* and *lac A*). The *lac Z* gene codes for β-galactosidase, which is responsible for the hydrolysis of lactose to glucose and galactose. The *lac Y* gene codes for permease, which allows lactose to enter the bacterium. The *lac p* region is the binding site for RNA polymerase during the initiation of transcription. The Lac I repressor protein is the product of the *lac I* gene and is constitutively expressed. Repressor proteins, when bound to the operator region, prevent binding of RNA polymerase to the promoter region, thus decreasing transcription of the *lac Z, lac Y,* and *lac A* genes. Culture of *E coli* in lactose-containing media causes a conformational change in the repressor protein, preventing its attachment to the operator region and increasing transcription of the *lac* operon structural genes.

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Culturing *E coli* in media containing glucose results in reduced expression of the *lac* operon, even when the media contains lactose as well. This occurs because the *lac* operon is positively regulated by the binding of catabolite activator protein (CAP) to a site slightly upstream from the promoter region. This only occurs when cAMP concentrations are high. Since glucose decreases the activity of adenylyl cyclase (reducing intracellular cAMP), the *lac* operon is repressed in high-glucose conditions. In summary, the *lac* operon is regulated by 2 distinct mechanisms:

1. Negatively by binding of the repressor protein to the operator locus
2. Positively by cAMP-CAP binding upstream from the promoter region

Mutations impairing the binding of the repressor protein to its binding site at the operator region will prevent repression of the genes of the *lac* operon in the absence of lactose. This results in increased transcription of the genes of the *lac* operon in lactose-deficient media, although the presence of glucose will prevent maximal transcriptional activity.

(Choices A and D) Mutations that impair the binding of cAMP-CAP to its regulatory site upstream from the promoter will decrease transcription of the *lac* operon, as cAMP-CAP is a positive regulator.

(Choices C and E) Mutations impairing the binding of RNA polymerase to the promotor region will also reduce transcription of the *lac* operon.

Educational objective:
The *lac* operon is regulated by two distinct mechanisms: negatively by binding of the repressor protein to the operator locus and positively by cAMP-CAP binding upstream from the promoter region. Constitutive expression of the structural genes of the *lac* operon occurs with mutations that impair the binding of the repressor protein (Lac I) to its regulatory sequence in the operator region.

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The *lac* operon is regulated by two distinct mechanisms: negatively by binding of the repressor protein to the operator locus and positively by cAMP-CAP binding upstream from the promoter region. Constitutive expression of the structural genes of the *lac* operon occurs with mutations that impair the binding of the repressor protein (Lac I) to its regulatory sequence in the operator region.

Biochemistry	Gastrointestinal & Nutrition	Lac operon
Subject	System	Topic

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Succinate dehydrogenase (SDH) is an enzyme complex located within the inner mitochondrial membrane that catalyzes the oxidation of succinate to fumarate. An experiment is conducted to determine if malate alters the rate of SDH activity. Reaction velocity is measured with and without a fixed quantity of malate as succinate concentration is gradually increased. Obtained results are shown below.

Succinate concentration (mM)	Rate of reaction without malate (μmol/L/sec)	Rate of reaction with malate (μmol/L/sec)
2	80	40
8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction
B. It binds the enzyme at a different site than succinate
C. It covalently binds the enzyme
D. It decreases affinity of the enzyme for succinate
E. It is a competitive inhibitor of the enzyme

Submit

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64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction (3%)

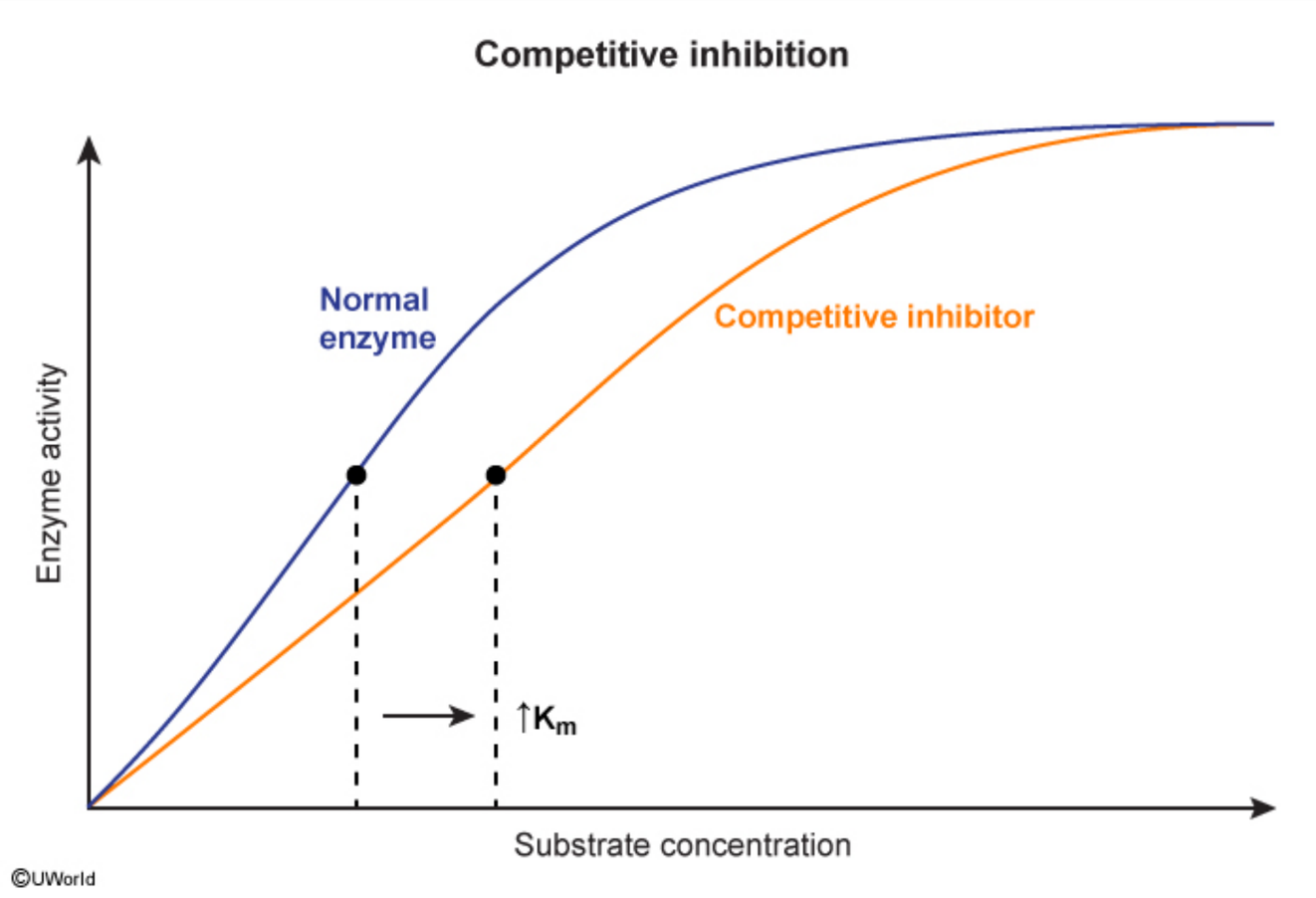
B. It binds the enzyme at a different site than succinate (8%)

C. It covalently binds the enzyme (1%)

D. It decreases affinity of the enzyme for succinate (10%)

✓ E. It is a competitive inhibitor of the enzyme (76%)

Omitted



The Michaelis-Menten model describes the behavior of enzyme-driven reactions by comparing the rate of reaction (V) to the concentration of the substrate (S). Maximal velocity (V_{max}) represents the speed at which the reaction occurs when the enzyme's active sites are completely saturated with substrate. The Michaelis constant (K_m) defines the substrate concentration at which half of the enzyme's binding sites are occupied by substrate (½ V_{max}). Substrates with high affinity for the enzyme typically have a low K_m.

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Competitive inhibition occurs when an inhibitor binds to an enzyme and prevents it from binding the substrate. Most competitive inhibitors (including malate) **bind at the active site** (substrate-binding pocket) and physically impede substrate binding. Because these inhibitors compete with the substrate for binding to the active site, additional substrate is required to reach ½ V_{max}, thereby **increasing apparent K_m**. Competitive inhibitors have no effect on enzyme function, and therefore **V_{max} is unchanged**.

In this example, V_{max} remains constant (at 400 μmol/L/sec) while K_m increases (from 8 to 16 mM) in the presence of malate. Therefore, malate is a competitive inhibitor of succinate dehydrogenase for succinate.

(Choice A) V_{max} depends on how fast an enzyme can catalyze a reaction when there are enough substrate molecules to fully saturate its active sites. Competitive inhibitors do not affect V_{max}, as higher substrate concentrations are able to overcome the inhibition.

(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). Noncompetitive inhibition does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

(Choice C) Irreversible inhibitors bind to enzymes through strong covalent bonds; this typically renders the enzyme permanently ineffective, decreasing the V_{max}.

(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the substrate remains unchanged.

Educational objective:
Competitive inhibitors compete with substrate for active binding sites on enzymes. Additional substrate is required to achieve the same rate of reaction, increasing the measured value of the Michaelis constant (K_m). Competitive inhibitors do not affect enzyme function; therefore, maximal velocity (V_{max}) is unchanged in their presence.

The Michaelis-Menten model describes the behavior of enzyme-driven reactions by comparing the rate of reaction (V) to the concentration of the

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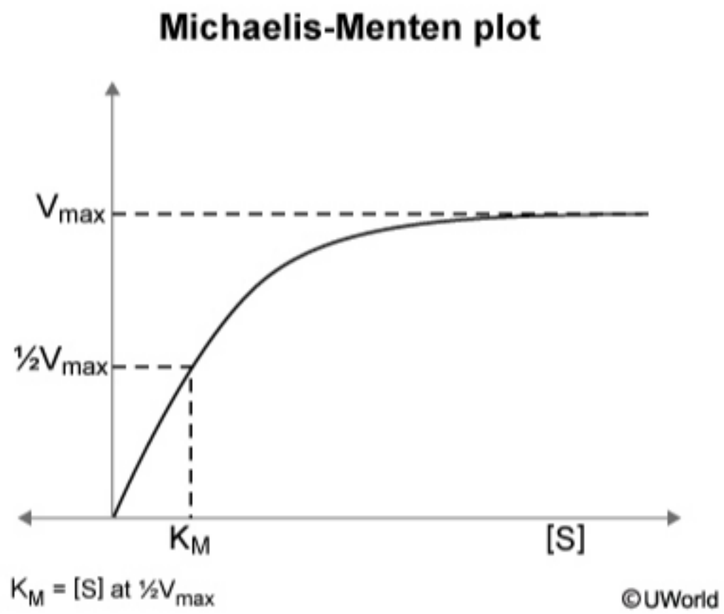

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Biochemistry	General Principles	Enzyme kinetics
Subject	System	Topic

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Competitive inhibition occurs when an inhibitor binds to an enzyme and prevents it from binding the substrate. Most competitive inhibitors

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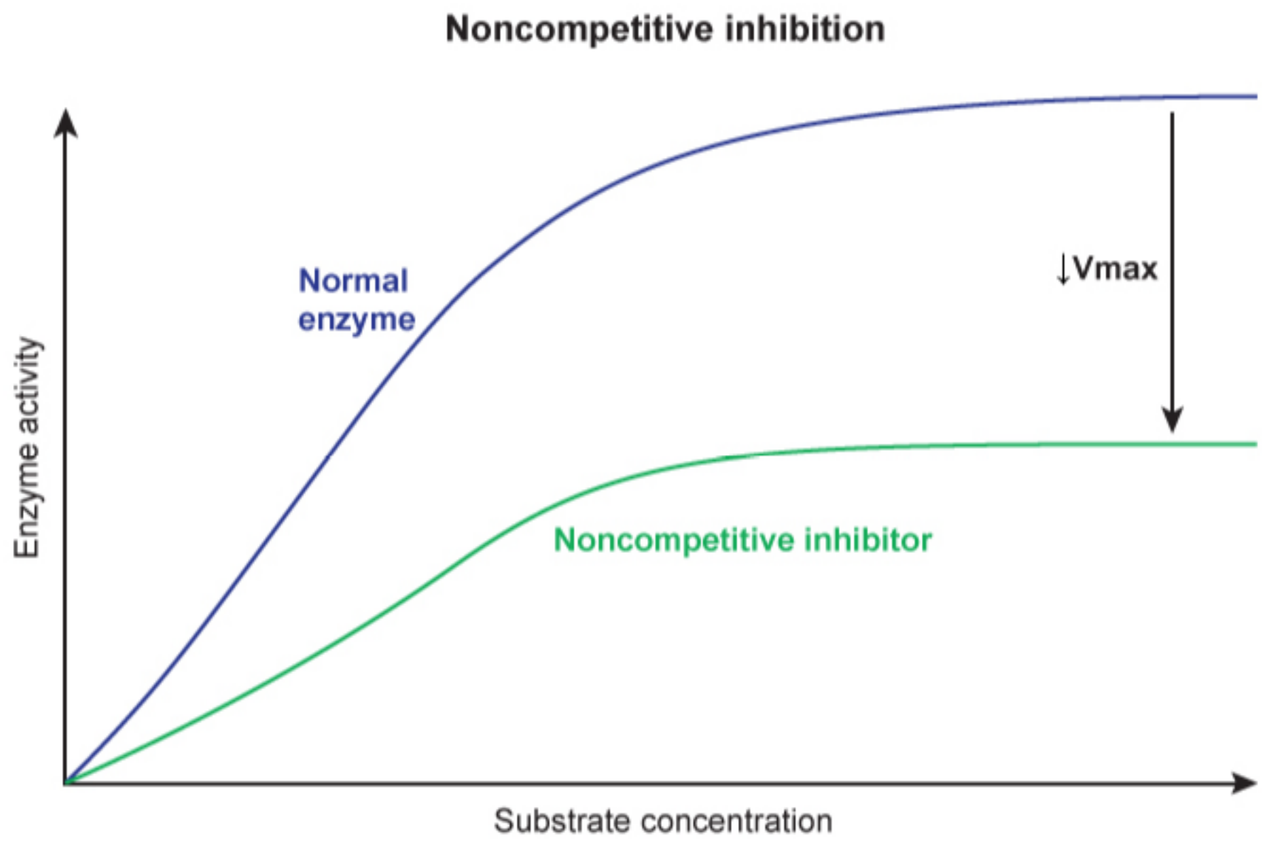

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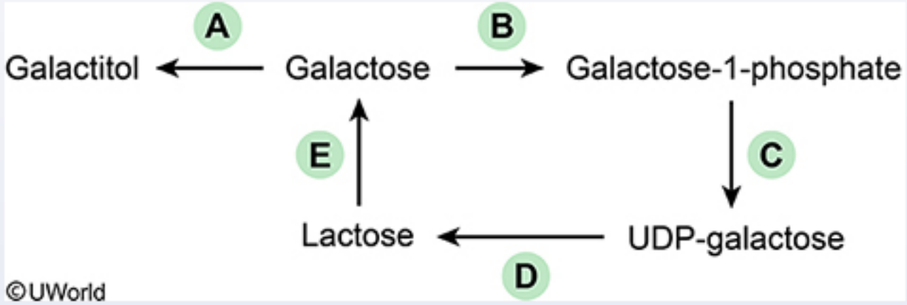
A 2-year-old boy who attends daycare is brought to the emergency department due to diarrhea, fatigue, and abdominal cramps. The parents also state that he has foul-smelling, frothy stools. The boy is admitted for rehydration and subsequently diagnosed with giardiasis, which is treated with metronidazole. He improves and is discharged home. One week after discharge, the boy is seen by the primary health care provider for recurrent symptoms of frothy, loose stools and abdominal bloating and cramping. Which of the following steps of this pathway is most likely impaired in this patient?



- A. A
- B. B
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- D. D
- E. E

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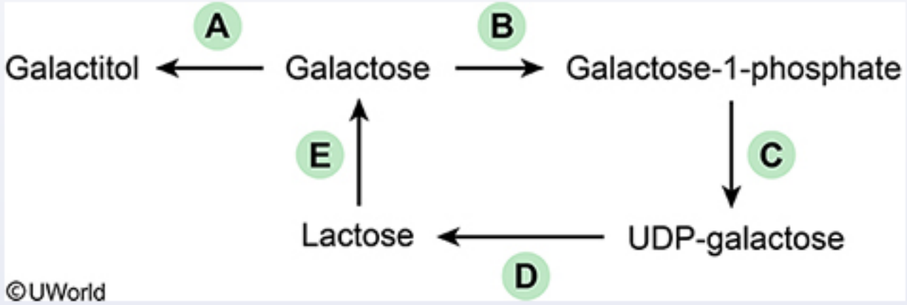

A. A (1%)
B. B (8%)
C. C (9%)
D. D (4%)
✓ E. E (75%)

Omitted
Correct answer
E

75%
Answered correctly

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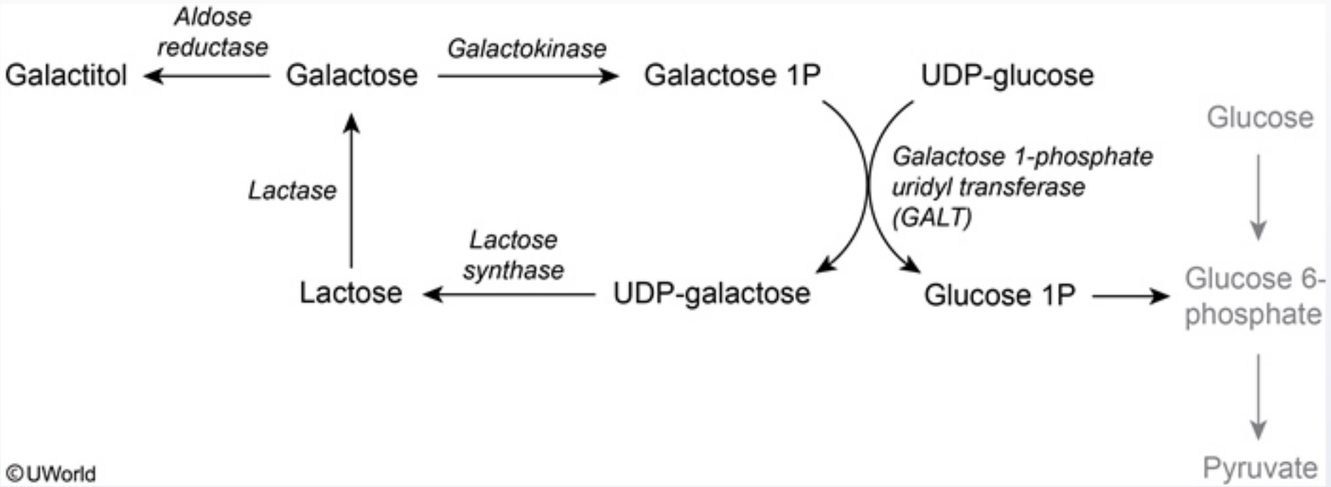

Lactose is a disaccharide present in milk and other dairy products that is normally hydrolyzed into glucose and galactose by lactase, a brush border enzyme concentrated in epithelial cells of the small intestine. **Lactose intolerance** is due to **decreased or absent lactase**. Malabsorbed lactose then enters the large intestine where it is fermented by bacteria, causing the clinical features of lactose intolerance: **diarrhea**, **flatulence**, and **abdominal bloating and cramping**.

Lactose intolerance can be either primary or secondary. Primary lactose intolerance is due to a genetically regulated reduction of lactase production, and its incidence increases with age. **Secondary** or acquired lactose intolerance can be due to **inflammation** (eg, celiac disease) or **infection** (eg, giardiasis) of the small intestine, both of which cause cellular damage to the intestinal lining. The damaged cells slough off and are replaced by immature cells with low lactase concentrations, resulting in a decreased ability to convert lactose to galactose. Secondary lactose intolerance is common after giardial infections.

(Choices A, B, and C) Galactose-1-phosphate uridyl transferase (GALT) deficiency causes the most severe and most common form of galactosemia. Symptoms occur within the first few days of life after initiation of breastfeeding or formula and include vomiting, jaundice, hepatomegaly, and lethargy. Excess galactose is converted to galactitol by aldose reductase, resulting in cataracts from excess galactitol deposition in the lens. Galactokinase deficiency is a less common type of galactosemia, causing cataract formation only.

(Choice D) Lactose synthase converts UDP-galactose to lactose within the mammary glands during milk formation. Deficiency of this enzyme

and abdominal bloating and cramping.

Lactose intolerance can be either primary or secondary. Primary lactose intolerance is due to a genetically regulated reduction of lactase production, and its incidence increases with age. **Secondary** or acquired lactose intolerance can be due to **inflammation** (eg, celiac disease) or **infection** (eg, giardiasis) of the small intestine, both of which cause cellular damage to the intestinal lining. The damaged cells slough off and are replaced by immature cells with low lactase concentrations, resulting in a decreased ability to convert lactose to galactose. Secondary lactose intolerance is common after giardial infections.

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(Choice D) Lactose synthase converts UDP-galactose to lactose within the mammary glands during milk formation. Deficiency of this enzyme does not result in lactose malabsorption.

Educational objective:
Secondary lactase deficiency can occur after inflammatory (eg, celiac disease) or infectious (eg, giardiasis) processes damage the microvilli of the small intestines. Clinical presentation includes abdominal distension and cramping, flatulence, and diarrhea.

References

- Lactose intolerance.
- Lactose intolerance in infants, children, and adolescents.
- Lactose malabsorption

Biochemistry	Gastrointestinal & Nutrition	Lactose intolerance
Subject	System	Topic

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A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the emergency department due to profound fevers and malaise. After initial evaluation, she is hospitalized for septicemia. Blood cultures plated on lactose-containing media grow rapidly dividing gram-negative bacteria. Replication of these microbial cells requires synthesis of two daughter strands of DNA using the parent strands as templates. Which of the following processes will differ the most between the 2 daughter strands formed at each replication fork?

A. Enzymatic function of DNA helicase

B. Interaction with single-stranded DNA-binding proteins

C. Joining of DNA fragments by ligase

D. Proofreading of the newly synthesized DNA

E. Relief of supercoils by topoisomerase

Submit

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- A. Enzymatic function of DNA helicase (2%)
- B. Interaction with single-stranded DNA-binding proteins (8%)
- ✓ C. Joining of DNA fragments by ligase (65%)
- D. Proofreading of the newly synthesized DNA (19%)
- E. Relief of supercoils by topoisomerase (3%)

Omitted
Correct answer
C

65%
Answered correctly

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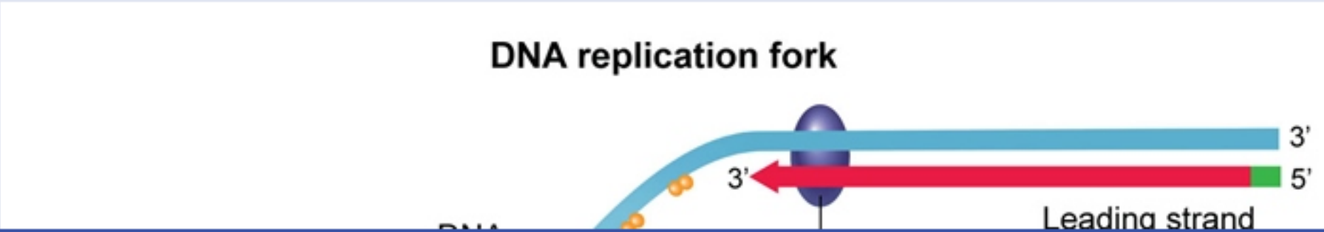
Explanation



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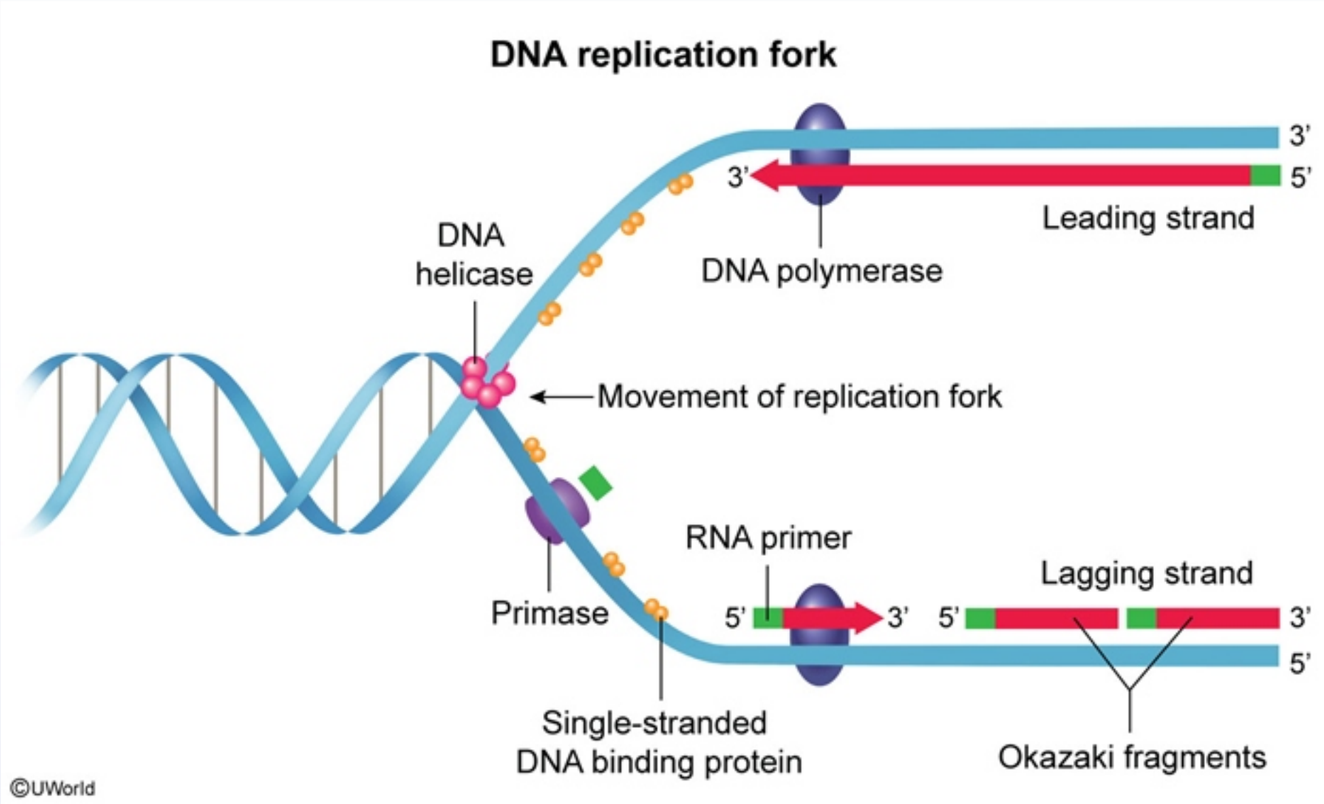

DNA replication is similar in prokaryotes and eukaryotes, with DNA polymerases I and III being the main polymerase enzymes involved in prokaryotic DNA replication. For DNA replication to begin, DNA helicase must first unwind the DNA double helix and separate the parent strands **(Choice A)**. The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA-binding proteins to prevent spontaneous reannealing **(Choice B)**.

Synthesis of the daughter strands occurs simultaneously from both parent strands. Because **DNA synthesis can occur only in the 5'→3' direction**, one daughter strand is synthesized continuously toward the replication fork (leading strand). However, the other strand must be synthesized **discontinuously** in a direction away from the replication fork (lagging strand), with more and more segments being added as the

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(Choice D) DNA polymerases I and III have proofreading ability (ie, 3'→5' exonuclease activity), and the proofreading function of these polymerases is not restricted to either the leading or lagging strand.

(Choice E) Topoisomerase II produces negative supercoiling in the DNA helix ahead of the replication fork to reduce the strain produced by unwinding, which causes positive supercoiling.

Educational objective:
DNA replication occurs in the 5'→3' direction on both strands. In contrast to the continuous synthesis of the leading strand, lagging strand synthesis occurs discontinuously and is composed of short stretches of RNA primer plus newly synthesized DNA segments (Okazaki fragments). As a result, lagging strand synthesis requires the repetitive action of DNA primase and DNA ligase.

References

- Timing, coordination, and rhythm: acrobatics at the DNA replication fork.

Biochemistry	General Principles	Dna replication
Subject	System	Topic

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

(Choice A). The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA-binding proteins to prevent spontaneous reannealing **(Choice B)**.

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Biochemistry	General Principles	Dna replication
Subject	System	Topic

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A 34-year-old woman comes to the physician with abdominal pain and melena. She also complains of progressive fatigue and a 5 kg (11 lb) weight loss over the last 2 months. She has a strong family history of colon, endometrial, and ovarian cancer. Colonoscopy shows a protuberant, friable mass in the ascending colon, and biopsy is diagnostic for colon adenocarcinoma. Genetic analysis confirms a mutation consistent with Lynch syndrome (hereditary nonpolyposis colon cancer). Which of the following is most likely responsible for the development of colon cancer in this patient?

A. Nucleotide mismatches that escape repair

B. Covalent bonds between adjacent pyrimidines

C. Insertion of abnormal bases (eg, uracil) into DNA

D. Empty sugar-phosphate residues in the DNA molecule

E. Double-strand breaks in DNA

Submit

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- ✓ A. Nucleotide mismatches that escape repair (89%)
- B. Covalent bonds between adjacent pyrimidines (1%)
- C. Insertion of abnormal bases (eg, uracil) into DNA (3%)
- D. Empty sugar-phosphate residues in the DNA molecule (0%)
- E. Double-strand breaks in DNA (5%)

Omitted
Correct answer
A

89%
Answered correctly

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Last Updated

Explanation

Lynch syndrome (hereditary nonpolyposis colon cancer) is an autosomal dominant disease caused by defective DNA mismatch repair. DNA replication occurs with a high degree of fidelity because mismatched nucleotides are repaired through the proofreading activity of DNA polymerases delta and epsilon. However, this proofreading functionality is not infallible; base substitutions and small insertion-deletion mismatches occur due to errors in base pairing every 10^8 bases on average. It is the function of the DNA mismatch repair system to fix these errors shortly after the daughter strands are synthesized. The mismatch repair system involves several genes, including MSH2 and MLH1, which

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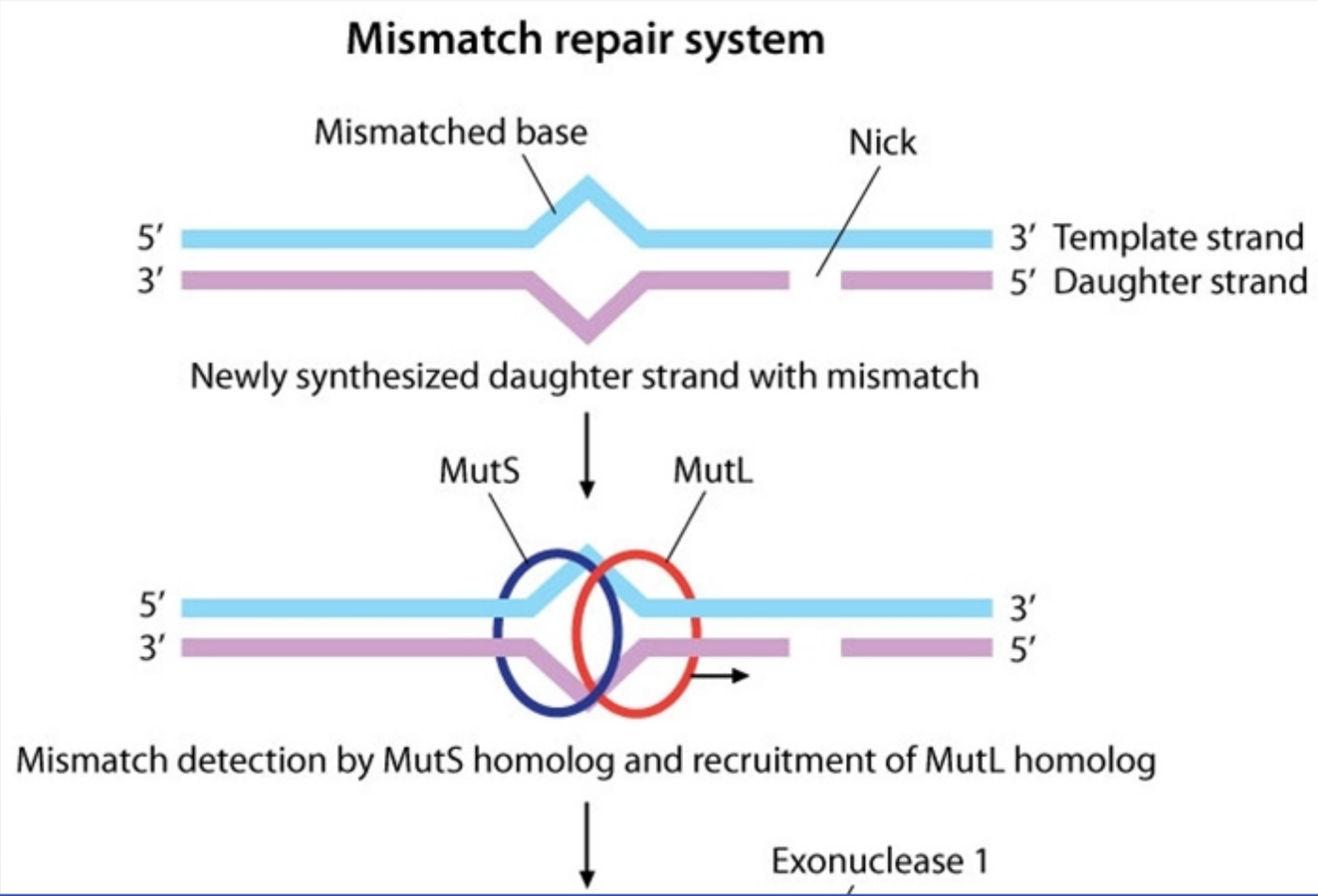

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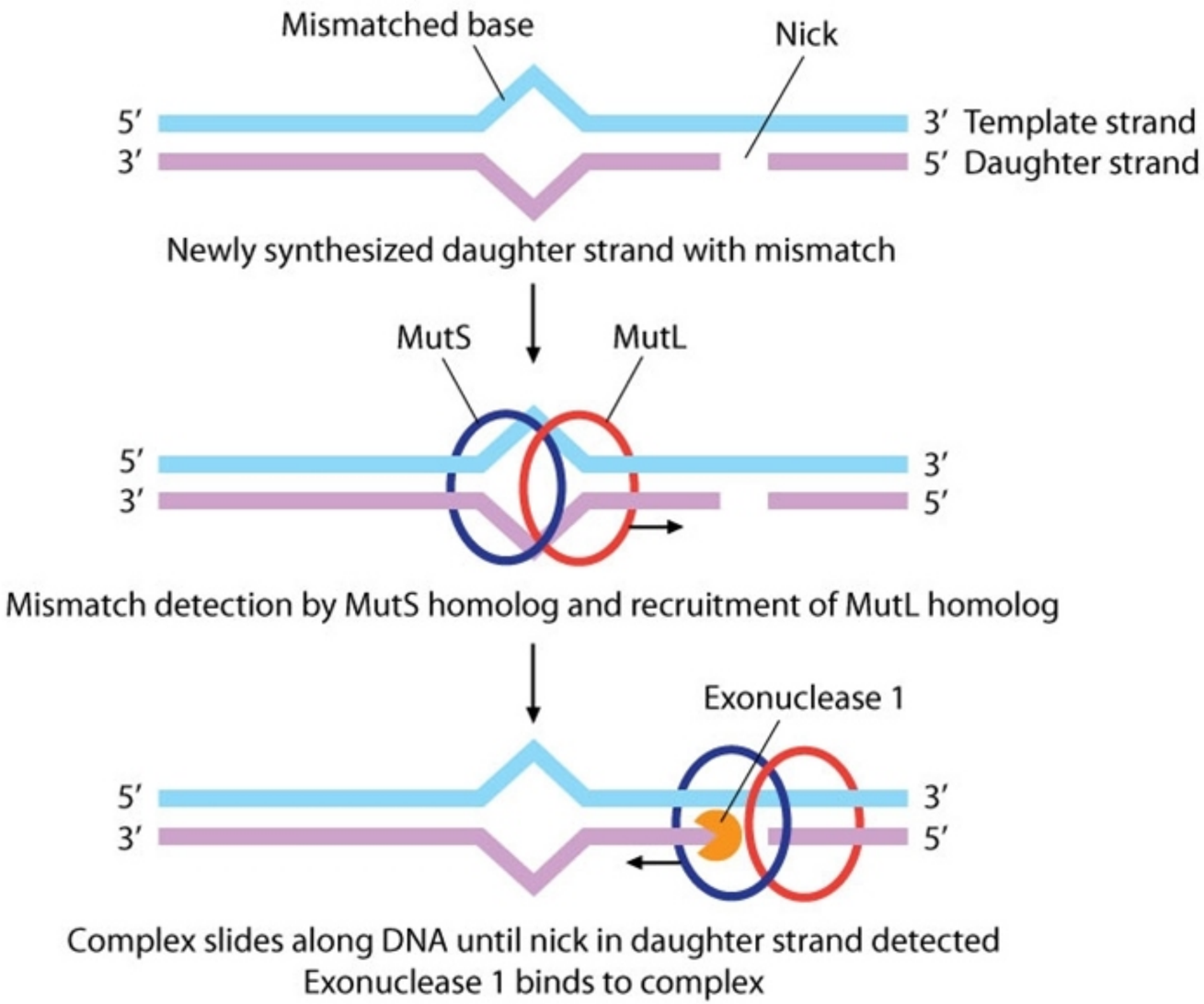
Mismatch repair system



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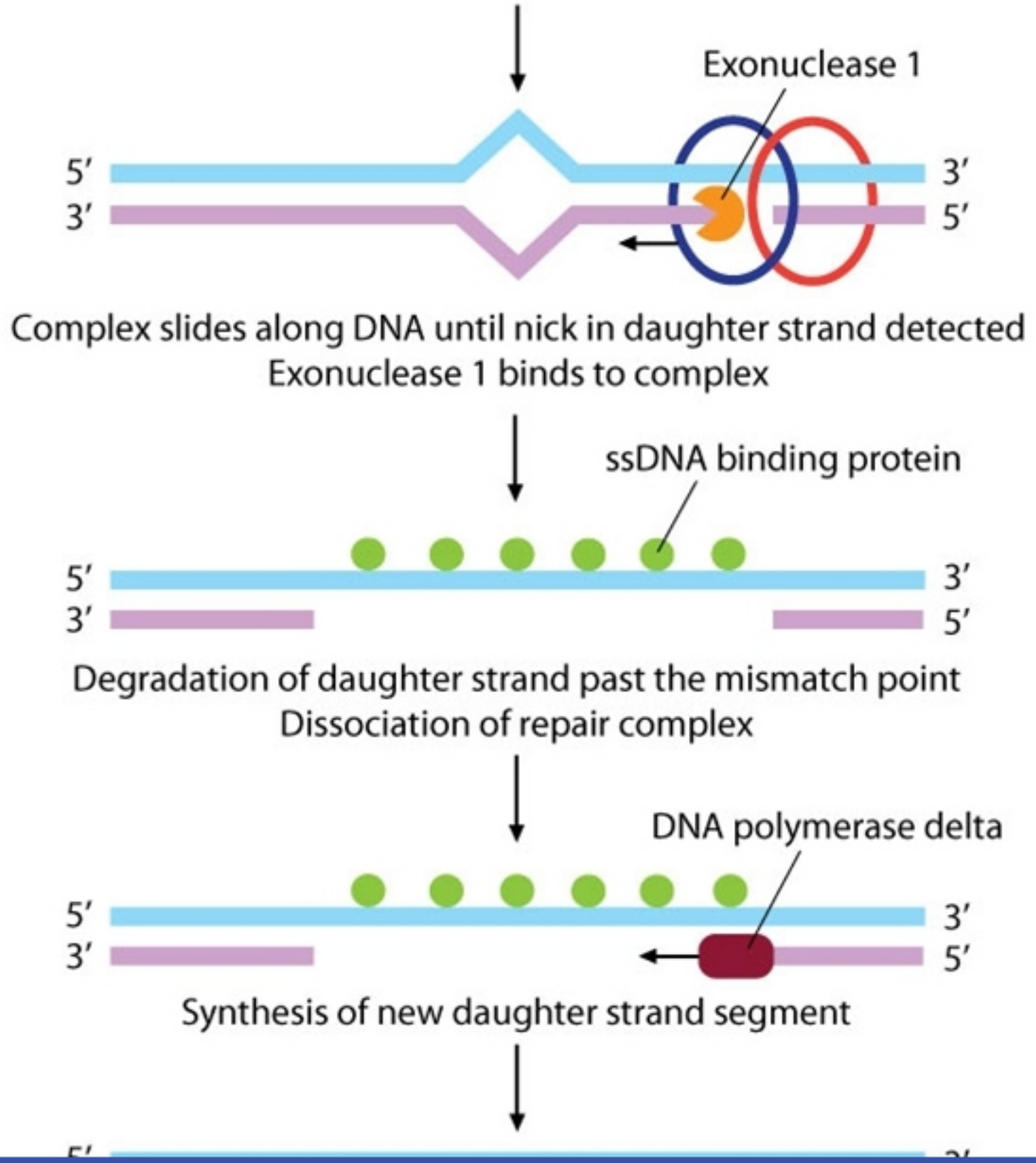

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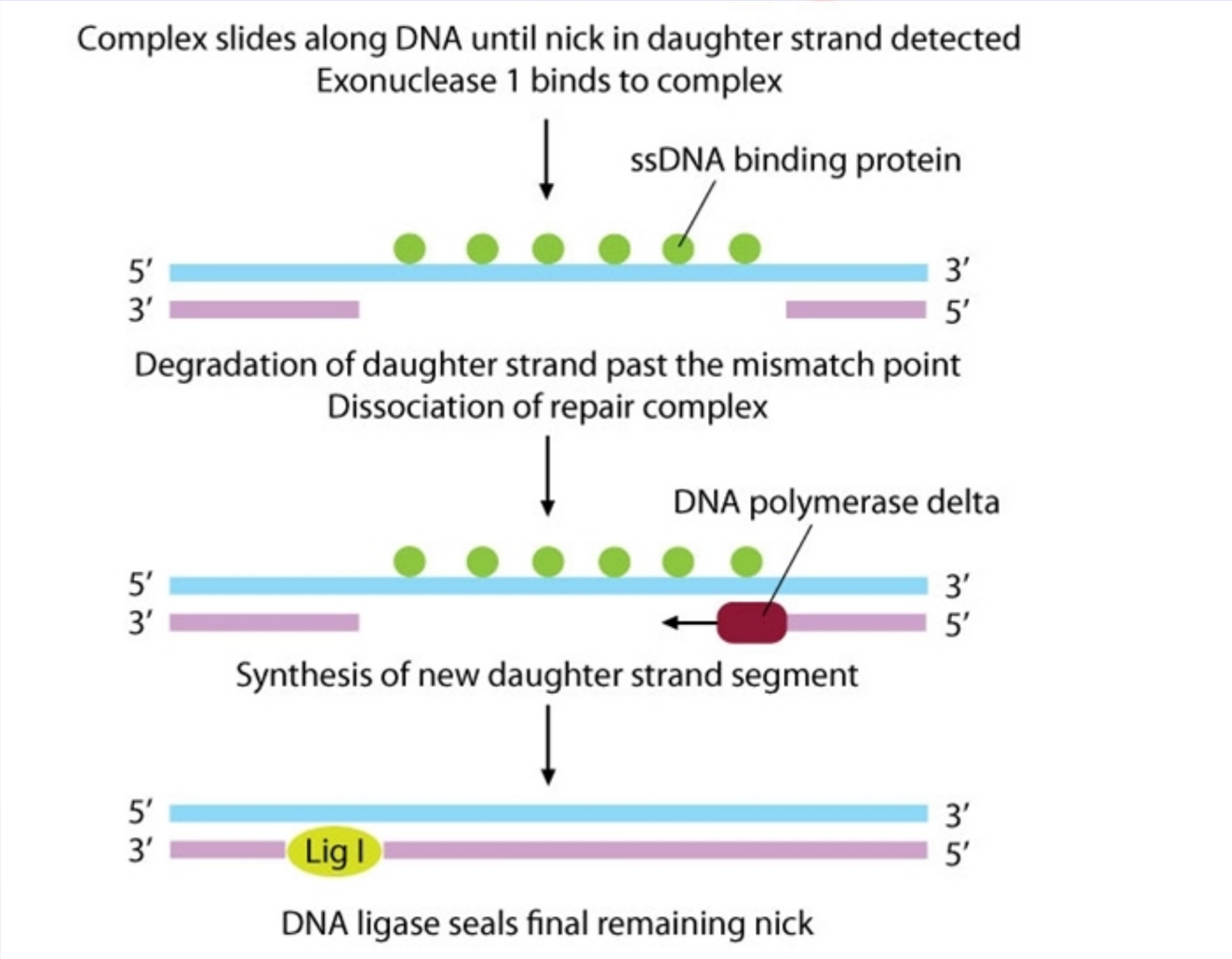

Mismatch repair begins with MutS homolog detecting a mismatch on the newly created daughter strand, which is distinguished from the parent strand by occasional nicks in the phosphodiester bonds. MutL homolog is then recruited, and the resulting complex slides along the DNA

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

DNA ligase seals final remaining nick

Mismatch repair begins with MutS homolog detecting a mismatch on the newly created daughter strand, which is distinguished from the parent strand by occasional nicks in the phosphodiester bonds. MutL homolog is then recruited, and the resulting complex slides along the DNA molecule until 1 of the daughter strand nicks is encountered. At this point, exonuclease 1 is loaded onto and activated by the repair complex. The daughter strand is then degraded backward past the initial mismatch point, leaving a variable gap of single-stranded DNA that is stabilized by ssDNA-binding protein. The complex then dissociates while DNA polymerase delta loads at the 3' end of the discontinuity and begins synthesizing a new daughter strand segment. Finally, DNA ligase I seals the remaining nick to complete the repair process.

(Choice B) Exposure to ultraviolet light can cause pyrimidine (usually thymine) dimers to form due to covalent joining of adjacent pyrimidines. Pyrimidine dimers interfere with DNA replication and are removed by nucleotide excision repair.

(Choices C and D) Several types of insults can alter the DNA bases. For example, nitrous acid can deaminate C, A, and G. There are also spontaneous changes, such as deamination of C to U and the constant low-level loss of purines via thermal disruption. Glycosylases are enzymes that detect and remove abnormal bases from DNA, creating an empty sugar-phosphate residue that is subsequently removed and replaced by the correct nucleotide (base excision repair).

(Choice E) Exposure to ionizing radiation causes double-stranded DNA breaks that are repaired by end-joining repair mechanisms. Non-homologous end joining, the main mechanism in primates, is more prone to cause mutations than homologous recombination.

Educational objective:
Lynch syndrome is an autosomal dominant disease caused by abnormal nucleotide mismatch repair. The mismatch repair system involves several genes, including MSH2 and MLH1, which code for components of the human MutS and MutL homologs. Mutations in these 2 genes account for around 90% of cases of Lynch syndrome.

Biochemistry	Gastrointestinal & Nutrition	Lynch syndrome
Subject	System	Topic

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A series of experiments is being conducted to determine the structure and function of different types of bacterial RNA. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of 90 nucleotides is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

- A. AUG
- B. CCA
- C. Methylguanosine triphosphate
- D. Poly-A
- E. TATA
- F. UAG

Submit

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- A. AUG (5%)
- ✓ B. CCA (41%)
- C. Methylguanosine triphosphate (5%)
- D. Poly-A (30%)
- E. TATA (3%)
- F. UAG (12%)

Omitted
Correct answer
B

41%
Answered correctly

03 secs
Time Spent

02/11/2020
Last Updated

Explanation

Secondary structure of tRNA

Secondary structure of tRNA

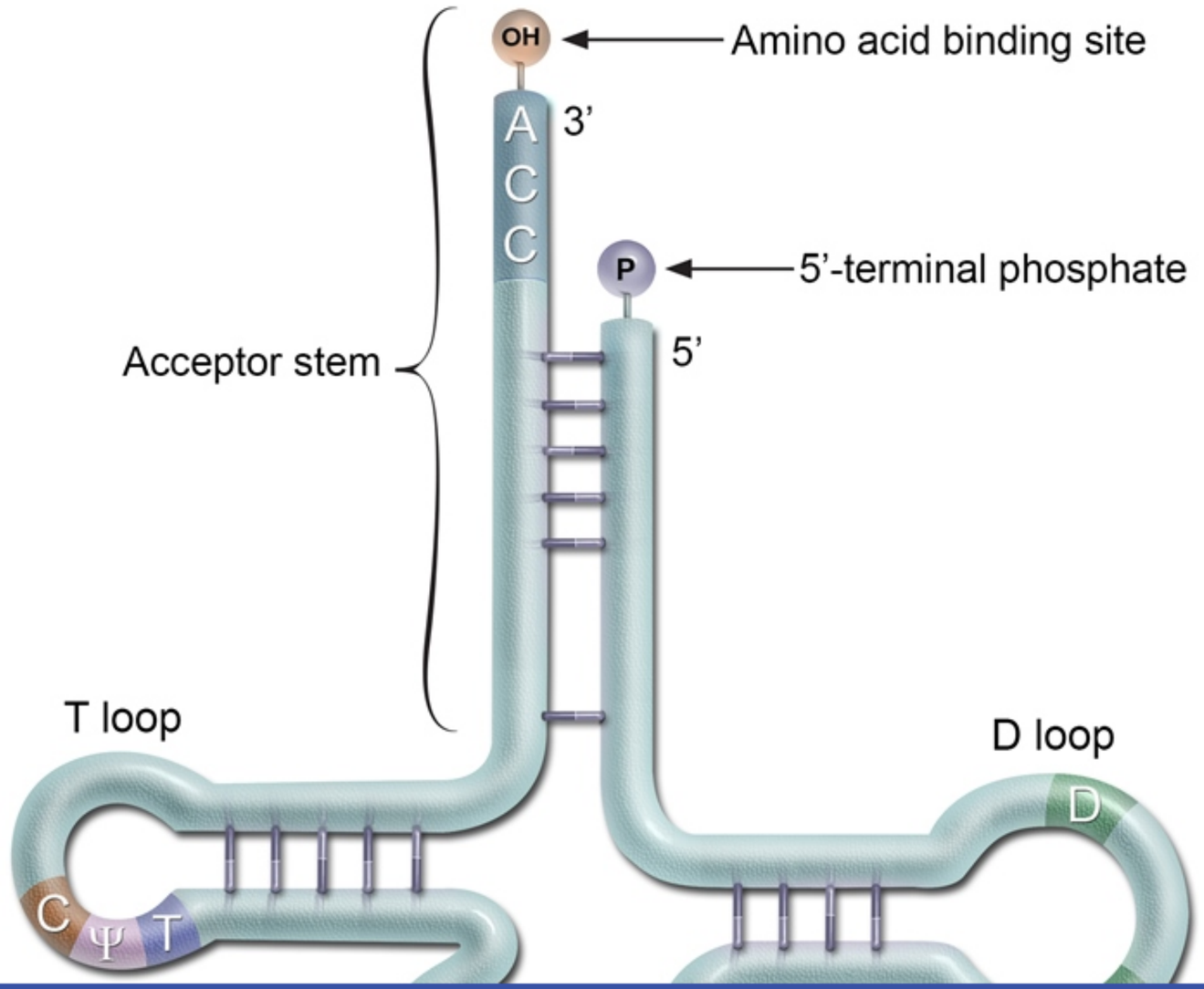
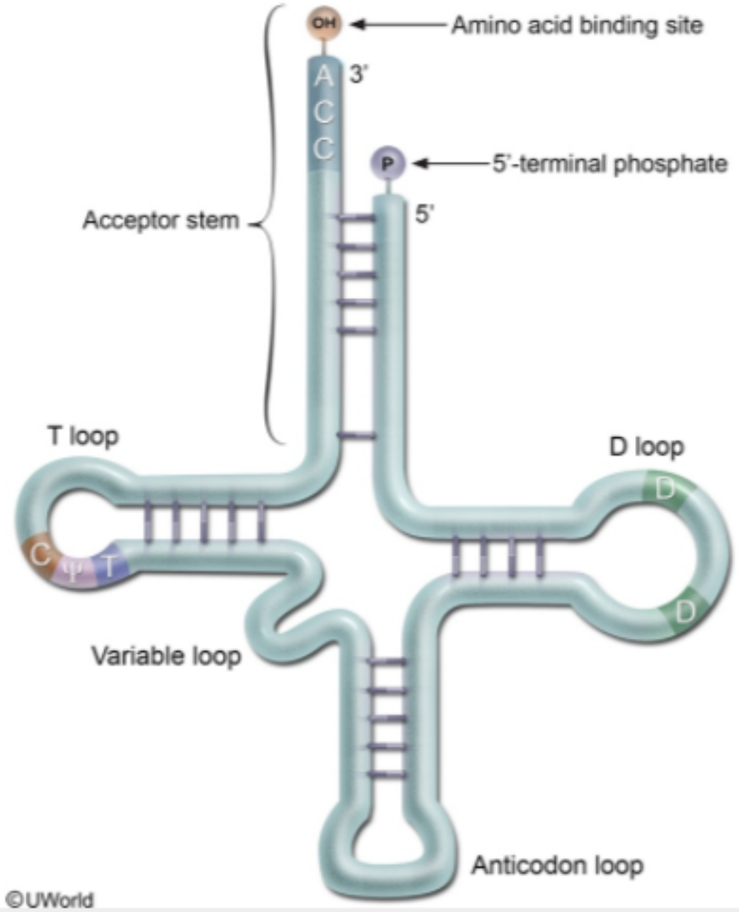


Exhibit Display

Secondary structure of tRNA



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Transfer RNA (tRNA) is a form of non-coding RNA composed of 74-93 nucleotides. Specific tRNAs transfer certain amino acid residues to the growing polypeptide during translation. tRNA functions by recognizing the 3 base codon on the mRNA being translated through its anticodon region, which contains complementary bases. The secondary structure of tRNA resembles a cloverleaf and contains the following regions:

- The **acceptor stem** is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. The CCA tail hangs off the 3' end, with the amino acid bound to the 3' terminal hydroxyl group. tRNA is "loaded" with the appropriate amino acid by aminoacyl tRNA synthetase. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- A **3' CCA tail** is added to the 3' end of tRNA as a posttranscriptional modification in eukaryotes and most prokaryotes. Several enzymes utilize this tail to help recognize tRNA molecules.
- The **D loop** contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- The **anticodon loop** contains sequences that are complementary to the mRNA codon. During translation, the ribosome complex selects the proper tRNA based solely on its anticodon sequence.
- The **T loop** contains the TΨC sequence that is necessary for binding of tRNA to ribosomes. The TΨC sequence refers to the presence of ribothymidine, pseudouridine, and cytidine residues.

(Choices A and F) AUG and UAG are mRNA start and stop codons that initiate and terminate translation, respectively.

(Choices C and D) After transcription, eukaryotic pre-mRNA undergoes posttranscriptional modification, which includes the addition of a poly-A tail at the 3' end and methylguanosine cap at the 5' end, and the removal of introns.

(Choice E) A TATA box is an upstream promoter region associated with some genes in eukaryotic organisms. TATA binding protein binds to this promoter during transcription, unwinding the DNA and initiating separation of the strands.

Educational objective:
Transfer RNA (tRNA) is a small, noncoding form of RNA that contains chemically modified bases (eg, dihydrouridine, ribothymidine, pseudouridine). tRNA has a CCA sequence at its 3'-end that is used as a recognition sequence by proteins. The 3' terminal hydroxyl group of the CCA tail serves as the amino acid binding site.

utilize this tail to help recognize tRNA molecules.

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References

- CCA addition to tRNA: implications for tRNA quality control.

Biochemistry	General Principles	Translation
Subject	System	Topic

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A genetic researcher is comparing the DNA replication process of prokaryotic and eukaryotic cells. In an experiment, *Escherichia coli* and human cells are cultured in separate media containing tagged nucleotides and their rates of DNA replication are determined. Although the eukaryotic genome is significantly larger and more complex than that of the prokaryote, eukaryotic DNA replication still occurs in a timely manner. Which of the following features of eukaryotic replication best explains this observation?

A. Continuous synthesis of the lagging strand

B. Energy-independent DNA unwinding

C. Multiple origins of replication

D. No proofreading of daughter strands

E. No requirement for RNA primers

Submit

A genetic researcher is comparing the DNA replication process of prokaryotic and eukaryotic cells. In an experiment, *Escherichia coli* and human cells are cultured in separate media containing tagged nucleotides and their rates of DNA replication are determined. Although the eukaryotic genome is significantly larger and more complex than that of the prokaryote, eukaryotic DNA replication still occurs in a timely manner. Which of the following features of eukaryotic replication best explains this observation?

- A. Continuous synthesis of the lagging strand (5%)
- B. Energy-independent DNA unwinding (2%)
- ✓ C. Multiple origins of replication (89%)
- D. No proofreading of daughter strands (0%)
- E. No requirement for RNA primers (1%)

Omitted
Correct answer
C

89%
Answered correctly

02 secs
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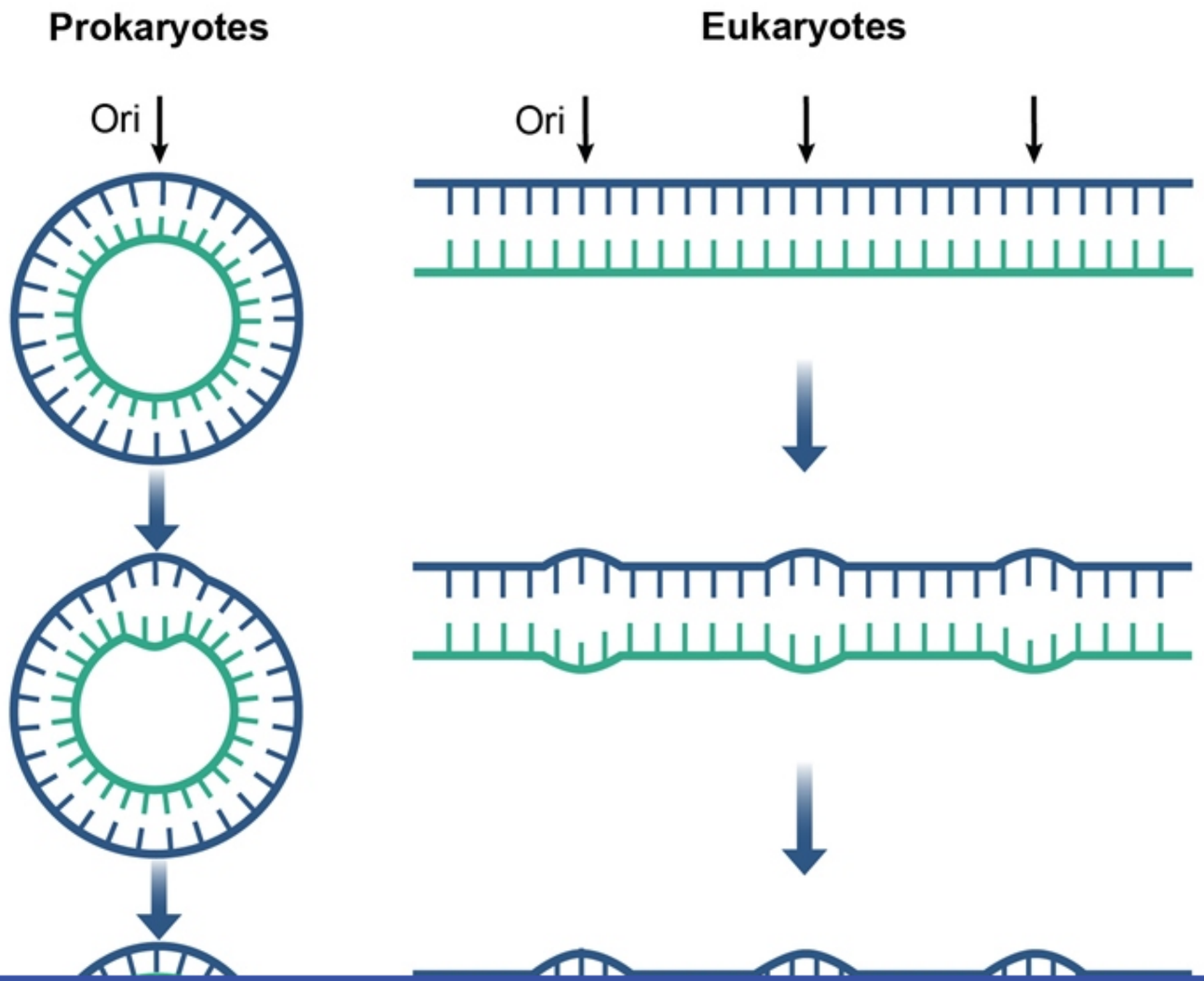
02/26/2020
Last Updated

Explanation

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Origin of replication (Ori)



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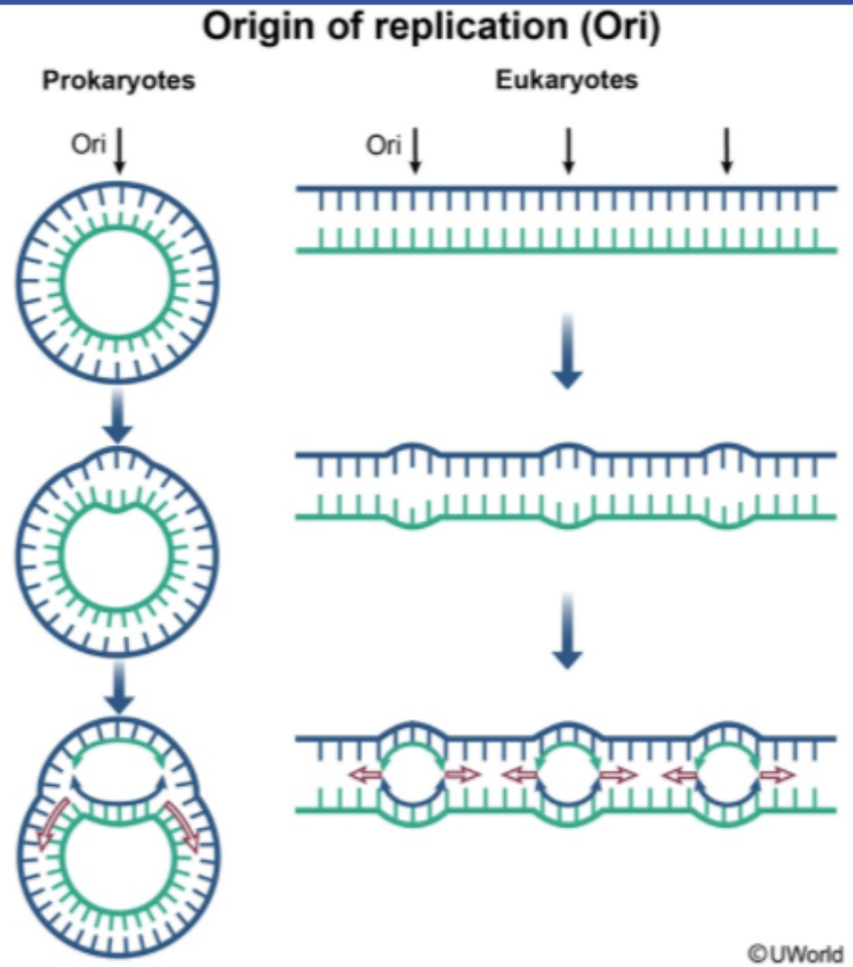

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The key steps of DNA replication are similar in eukaryotes and prokaryotes (eg, *Escherichia coli*) and are as follows:

1. Unwinding of double-stranded DNA by helicase to produce single-stranded DNA
2. Formation of a replication fork
3. Synthesis of RNA primers by the enzyme primase
4. Synthesis and concurrent proofreading of daughter DNA strands by DNA polymerases
5. Removal and replacement of RNA primers with DNA
6. Ligation of Okazaki fragments on lagging strands by the enzyme ligase

Despite the similarities of prokaryotic and eukaryotic DNA replication, there are important differences between these processes. Prokaryotes possess 3 major DNA polymerases (I, II, and III), whereas eukaryotes have 5 major DNA polymerases (α, β, γ, δ, and ε). The **eukaryotic genome** is also much larger and more complex than the prokaryotic genome, which can be partly explained by the abundance of noncoding DNA regions (introns) located between coding regions (exons). In addition, prokaryotes typically have circular DNA with a single origin of replication, whereas eukaryotes have linear DNA with **multiple origins of replication**. This feature allows the eukaryotic genome to be copied in a quick and effective manner despite its large size.

(Choice A) Eukaryotic and prokaryotic DNA polymerases synthesize daughter strand DNA in the 5' to 3' direction. The leading strand is formed continuously, whereas the lagging strand is formed discontinuously, creating Okazaki fragments.

(Choice B) DNA unwinding is an energy-dependent process performed by the enzyme helicase in both prokaryotes and eukaryotes.

(Choice D) Proofreading of daughter strands during DNA replication is necessary to preserve the genetic code and prevent potentially lethal mutations. All 3 prokaryotic DNA polymerases and most eukaryotic DNA polymerases (eg, γ, δ, ε) possess 3' to 5' exonuclease ("proofreading") activity.

(Choice E) Prokaryotic and eukaryotic DNA polymerases require an RNA primer before they can initiate synthesis of complementary DNA on a single-stranded template. Primase (prokaryotes) and DNA polymerase α (eukaryotes) are the enzymes responsible for synthesizing this primer.

Educational objective:
Multiple origins of replication make eukaryotic DNA replication quick and effective despite the large size and complexity of the genome compared

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Educational objective:
Multiple origins of replication make eukaryotic DNA replication quick and effective despite the large size and complexity of the genome compared to that of prokaryotic organisms.

References

- Mechanism of chromosomal DNA replication initiation and replication fork stabilization in eukaryotes.

Biochemistry	General Principles	Dna replication
Subject	System	Topic

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Despite the similarities of prokaryotic and eukaryotic DNA replication, there are important differences between these processes. Prokaryotes

Exhibit Display

Function of prokaryotic & eukaryotic DNA polymerases

Organism	DNA polymerase	Function
Prokaryote	I	• Removes & replaces RNA primer with DNA • Proofreads DNA
	II	• Repairs DNA • Proofreads DNA
	III	• Leading & lagging strand DNA synthesis • Proofreads DNA
Eukaryote	α	• Synthesizes RNA primer • Initiates DNA synthesis
	β	• Repairs DNA
	γ	• Replicates mitochondrial DNA • Proofreads DNA
	δ	• Elongates Okazaki fragments • Proofreads DNA
	ε	• Elongates leading strand • Proofreads DNA

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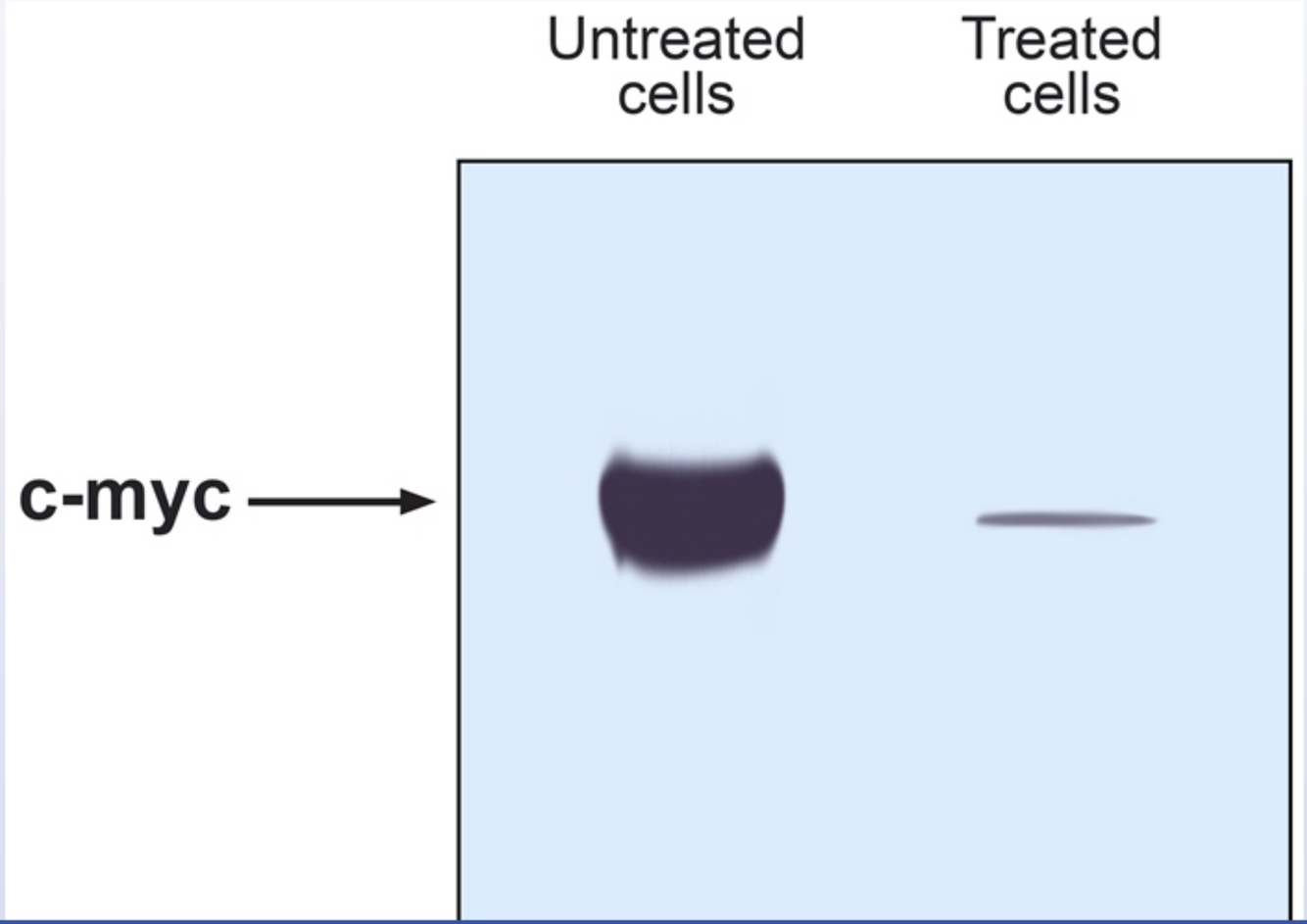
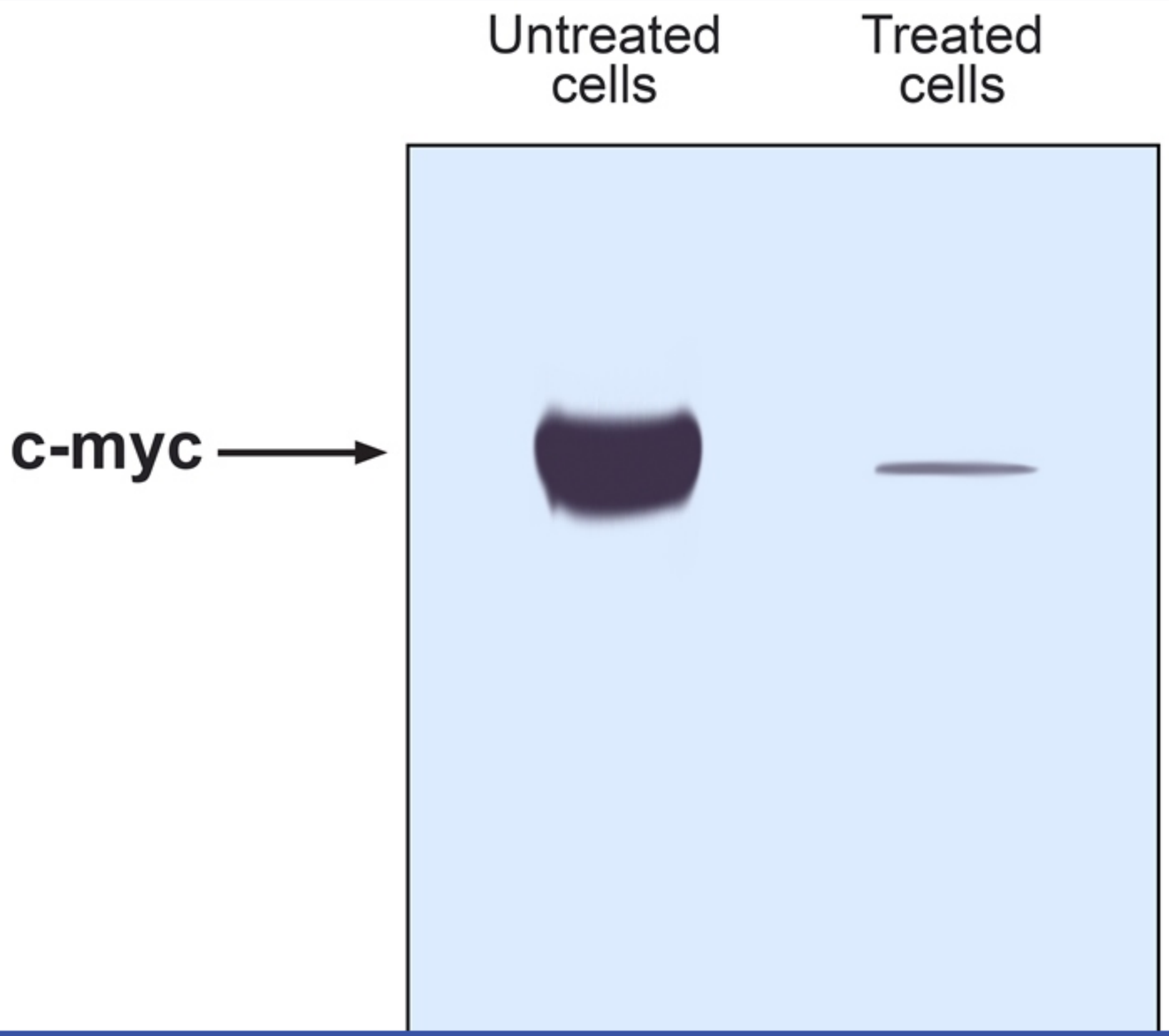
A pharmaceutical corporation investigating new therapeutic agents for treatment of Burkitt lymphoma synthesizes a double-stranded RNA molecule that is 21 base pairs in length. The RNA molecule has a base pair sequence that is complementary to a region of mRNA encoding c-Myc. Introduction of the RNA molecule into tumor cells results in a significant reduction in cell growth. Western blot analysis of equivalent numbers of treated and untreated cells is shown below.




Untreated cells
Treated cells
c-myc

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Which of the following processes was most likely directly interrupted in the cells exposed to the RNA molecule?

- A. DNA replication
- B. DNA transcription
- C. mRNA translation
- D. Proteasome activity
- E. Splicing

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Which of the following processes was most likely directly interrupted in the cells exposed to the RNA molecule?

- A. DNA replication (8%)
- B. DNA transcription (17%)
- ✓ C. mRNA translation (64%)
- D. Proteasome activity (3%)
- E. Splicing (5%)

Omitted
Correct answer

64%
Answered correctly

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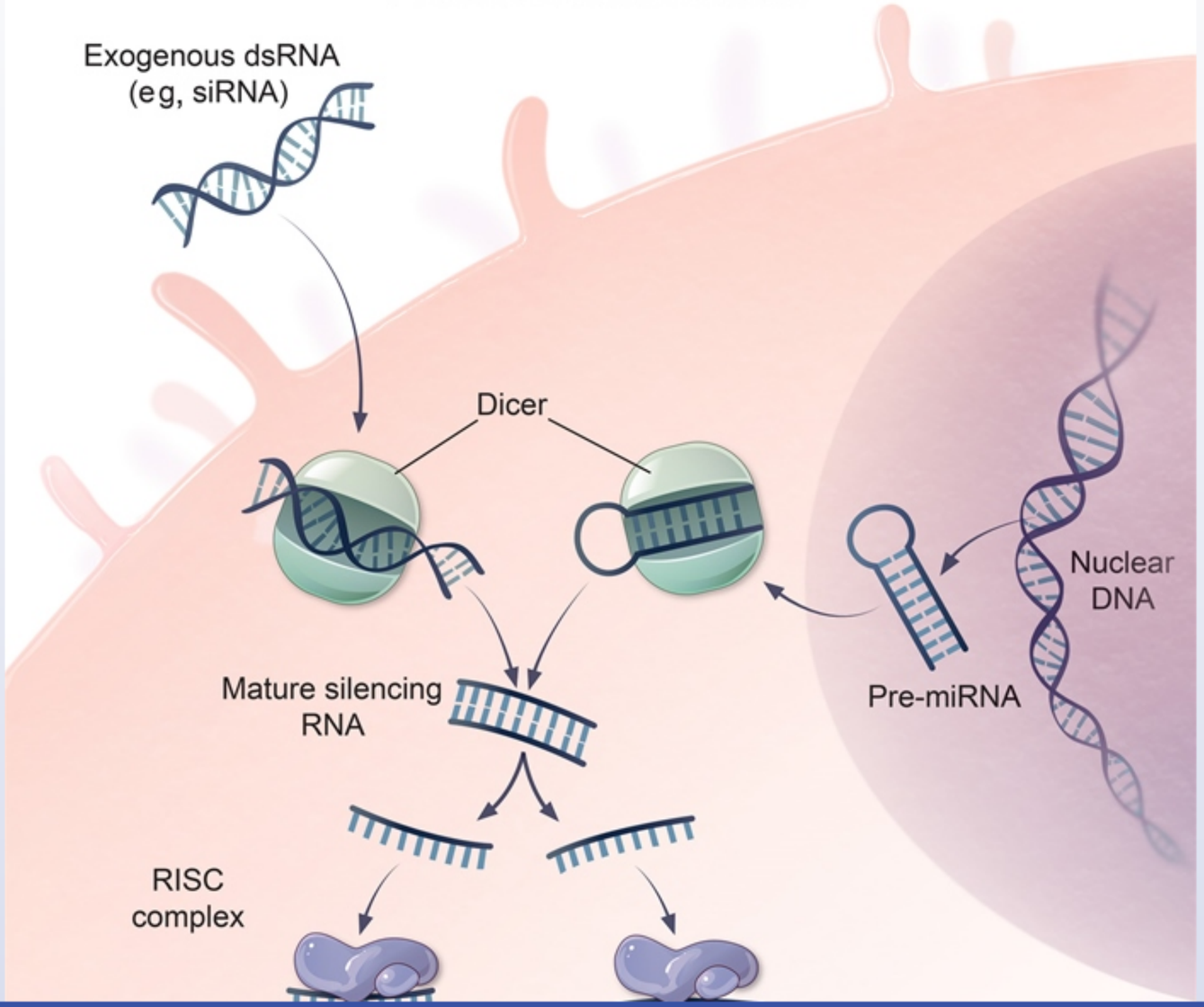
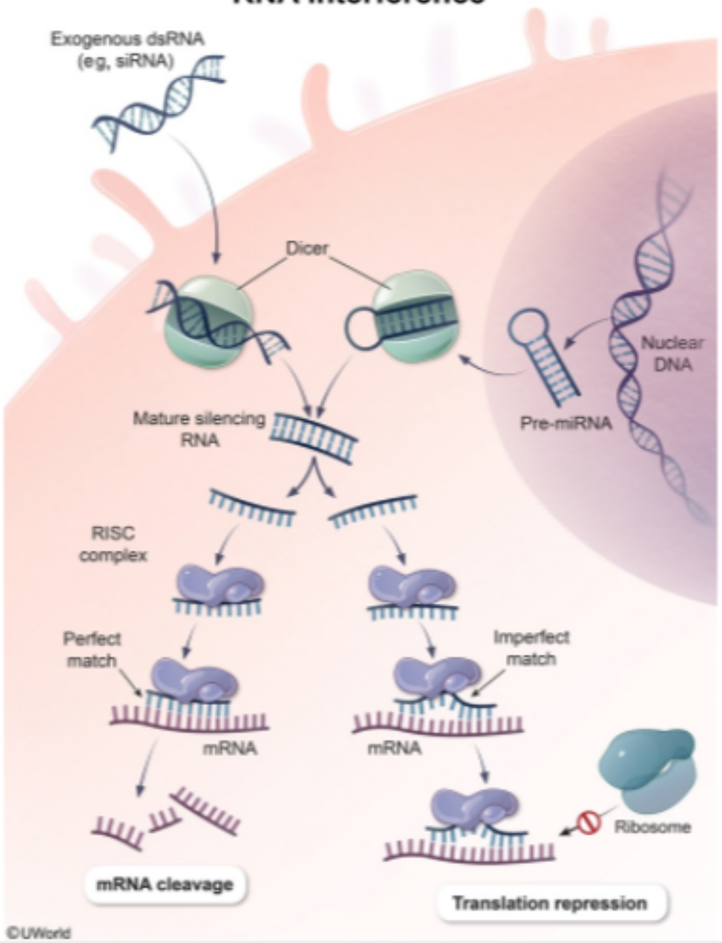
RNA interference



RNA interference

Exhibit Display

RNA interference



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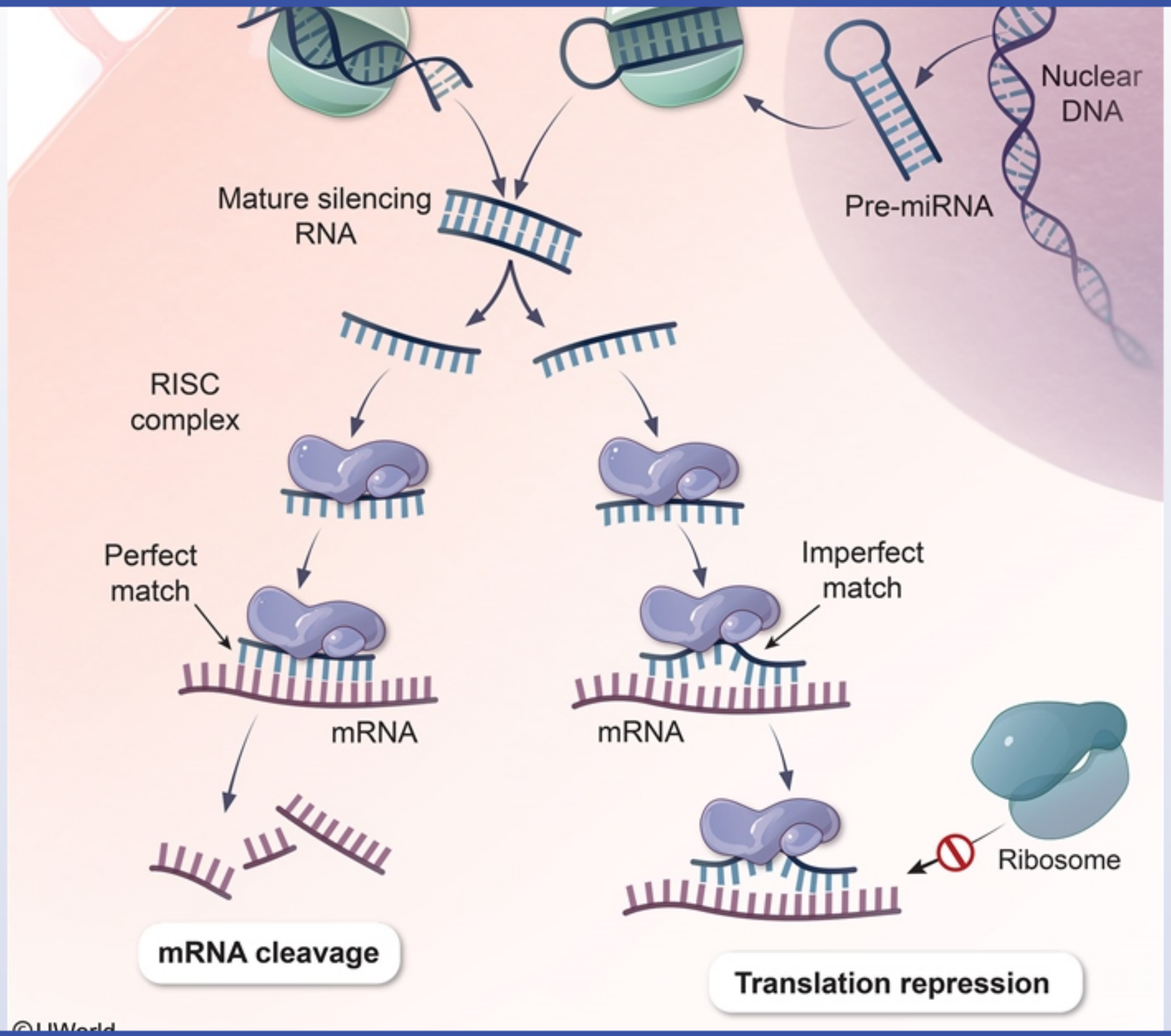
Nuclear DNA
Pre-miRNA
Mature silencing RNA
RISC complex
Perfect match
Imperfect match
mRNA
mRNA
Ribosome
mRNA cleavage
Translation repression

The results of the western blot show that the treated cell line produces less c-myc protein. This is most likely due to RNA interference, a mechanism by which short (20-30 base pair) **double-stranded RNA** sequences induce **posttranscriptional gene silencing**.

Silencing RNA includes both small interfering RNA (siRNA) and microRNA (miRNA). The human genome encodes over 1000 miRNA genes, each one capable of repressing hundreds of target genes; altered expression of miRNA genes are involved in the development of many diseases, including hematologic and solid malignancies. In addition, synthetic siRNA sequences can be introduced into cells to silence specific pathogenic genes (eg, c-Myc oncogene) and are being explored as possible **therapeutic agents**.

After being transcribed, miRNA undergoes processing in the nucleus to form a **double-stranded** precursor that is then exported into the cytoplasm. There, the precursor is cleaved into a short RNA helix by a ribonuclease protein called **dicer**. The individual strands are then separated and incorporated into RNA-induced silencing complex (RISC). This multiprotein complex uses its associated miRNA as a template to bind to complementary sequences found on target mRNAs. An exact match generally results in **mRNA degradation**, but a partial match also causes **translational repression** by preventing ribosome and translation factor binding.

(Choice A) DNA polymerase requires a short nucleic acid sequence primer for initiation of DNA synthesis. During DNA replication, these primers are formed from RNA bases by the enzyme DNA primase.

(Choice B) DNA transcription is the process in which RNA is transcribed from a DNA template by an RNA polymerase enzyme. Although certain miRNA sequences can cause transcriptional inhibition, posttranscriptional silencing is the predominant means of RNA interference.

(Choice D) Degradation of proteins and polypeptides occurs in proteasomes and lysosomes. Proteasomes mainly degrade nuclear and cytoplasmic proteins; lysosomes degrade cellular organelles and extracellular proteins.

(Choice E) Small nuclear RNA (snRNA) molecules bind to specific proteins to form small nuclear ribonucleoproteins (snRNPs). These snRNPs associate with pre-mRNA to form spliceosomes, which function to remove introns from pre-mRNA during processing within the nucleus.

Educational objective:
Short non-coding RNA sequences (eg, microRNA and small interfering RNA) induce posttranscriptional gene silencing by base-pairing with complementary sequences within target mRNA molecules.

References

- Origins and mechanisms of miRNAs and siRNAs

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References

- Origins and mechanisms of miRNAs and siRNAs.

Biochemistry	General Principles	Translation
Subject	System	Topic

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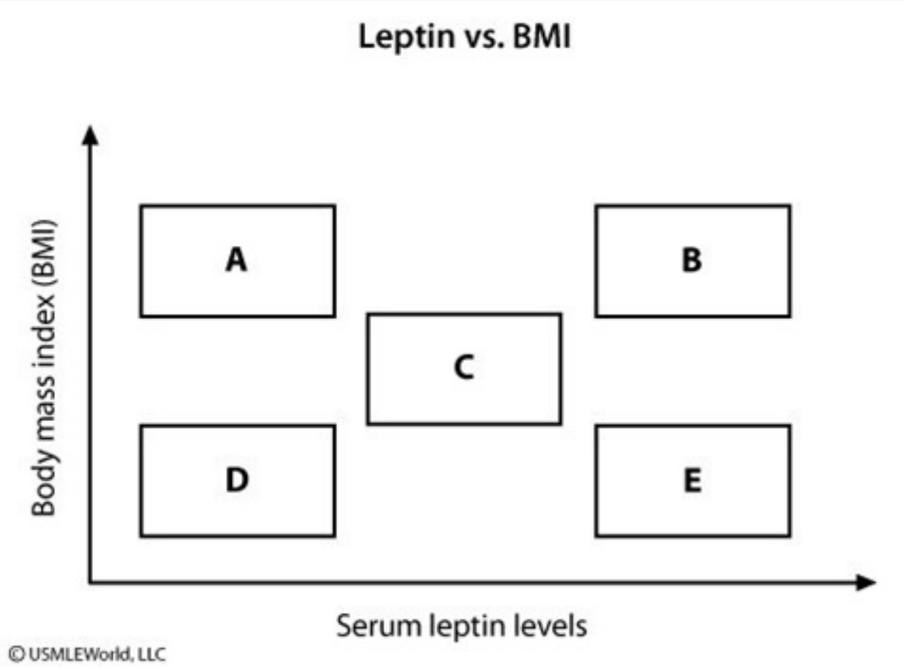
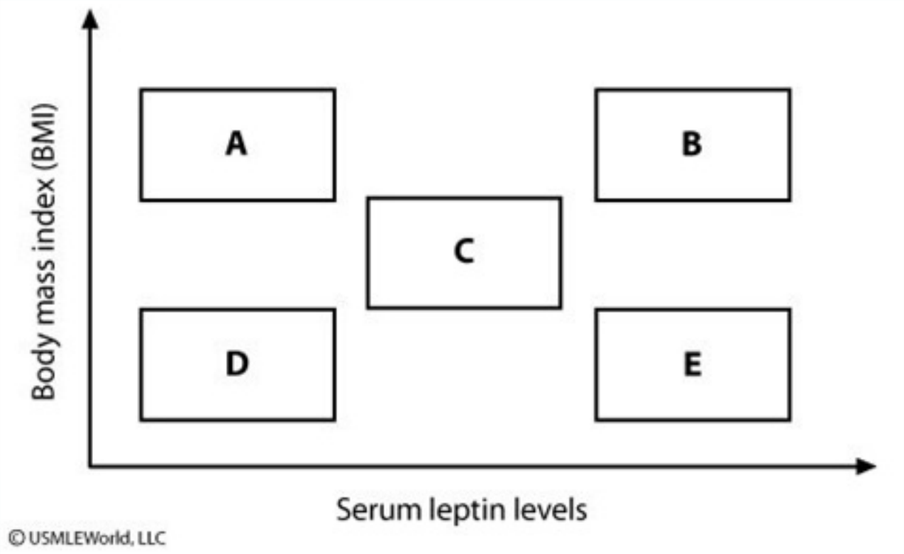
An investigator is studying weight regulation using experimental mouse models. Knockout mice are created with a homozygous mutation in the gene coding for the leptin receptor. This mutation prevents the receptor from binding leptin and initiating its normal signaling cascade. The knockout mice are allowed to feed at will, and their body mass index (BMI) and serum leptin levels are measured and compared with control mice. On the graph below, area C represents the normal relationship between BMI and leptin in a control mouse.



Which of the following areas represents the expected relationship between BMI and serum leptin levels in a leptin receptor mutant mouse?

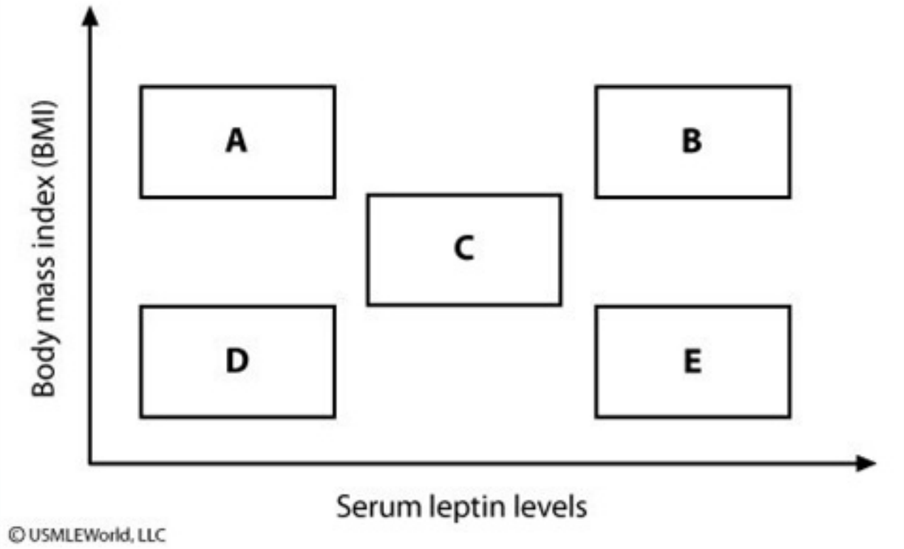
- A. A
- B. B
- C. C



Which of the following areas represents the expected relationship between BMI and serum leptin levels in a leptin receptor mutant mouse?

- A. A
- B. B
- C. C
- D. D
- E. E

Submit



Which of the following areas represents the expected relationship between BMI and serum leptin levels in a leptin receptor mutant mouse?

- A. A (15%)
- ✓ B. B (68%)
- C. C (1%)
- D. D (3%)
- E. E (10%)

Omitted
Correct answer

68%
Answered correctly

04 secs
Time Spent

01/26/2020
Last Updated

Explanation

Leptin is a protein hormone that plays an important role in regulating appetite and metabolism. It is produced primarily in adipocytes, and large fat cells produce more leptin than small ones. Serum leptin concentrations are highly correlated with body fat content.

Leptin decreases food intake in the following important ways:

1. Leptin decreases the production of neuropeptide Y, a potent appetite stimulant, in the arcuate nucleus of the hypothalamus.
2. Leptin stimulates the production of proopiomelanocortin (POMC) in the arcuate nucleus. Alpha-melanocyte-stimulating hormone (alpha-MSH) is produced by cleavage of POMC and inhibits food intake.

The knockout mouse described is homozygous for a mutation in the gene encoding the leptin receptor (db/db), resulting in ineffective leptin signaling. As a result, these mice become hyperphagic and profoundly obese. As leptin production is normal in these mice, leptin levels are elevated due to the increased lipocyte mass. In contrast, mice that are homozygous for a mutation resulting in impaired leptin production (ob/ob) also become hyperphagic and profoundly obese, but their leptin levels are low **(Choice A)**.

Human obesity resulting from mutations in the leptin receptor and the leptin gene has been described. However, most obese individuals do not have either of these mutations. Instead, it is thought that the sustained elevation in leptin levels from the enlarged fat stores results in leptin desensitization. Thus, obese individuals become resistant to the effects of leptin in a manner similar to the development of insulin resistance in type 2 diabetes.

(Choice D) Low leptin and low BMI correlate with low adipocyte stores and may be seen after prolonged starvation.

(Choice E) With intact receptor signaling, elevated leptin levels (ie, from exogenous leptin administration) would result in weight loss.

Educational objective:
Leptin is a protein hormone produced by adipocytes in proportion to the quantity of fat stored. Leptin acts on the arcuate nucleus of the hypothalamus to inhibit production of neuropeptide Y (decreasing appetite) and stimulate production of alpha-MSH (increasing satiety). Mutations in the leptin gene or receptor result in hyperphagia and profound obesity.

References

- Leptin receptors.

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References

- Leptin receptors.

Biochemistry	Gastrointestinal & Nutrition	Obesity
Subject	System	Topic

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An 11-year-old girl is evaluated for blurry vision. The patient was adopted internationally at age 9. She has no history of head or eye trauma or exposure to ionizing radiation. Motor and cognitive milestones have been achieved at the appropriate age. She has a good appetite and does not follow any specific diet. The patient takes no medications and has no allergies. Vaccinations are up to date. Vital signs are normal. She is at the 40th percentile for height and weight. Other than bilateral lens opacities, the rest of her examination is normal. Urine is positive for reducing substances. Deficient activity of which of the following enzymes is the most likely cause of this patient's eye condition?

- A. Aldolase B
- B. Alpha-galactosidase A
- C. Fructokinase
- D. Galactokinase
- E. Glucose-6-phosphatase
- F. Hexosaminidase A
- G. Sphingomyelinase

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- A. Aldolase B (20%)
- B. Alpha-galactosidase A (6%)
- C. Fructokinase (10%)
- ✓ D. Galactokinase (52%)
- E. Glucose-6-phosphatase (2%)
- F. Hexosaminidase A (4%)
- G. Sphingomyelinase (2%)

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Correct answer
D

52%
Answered correctly

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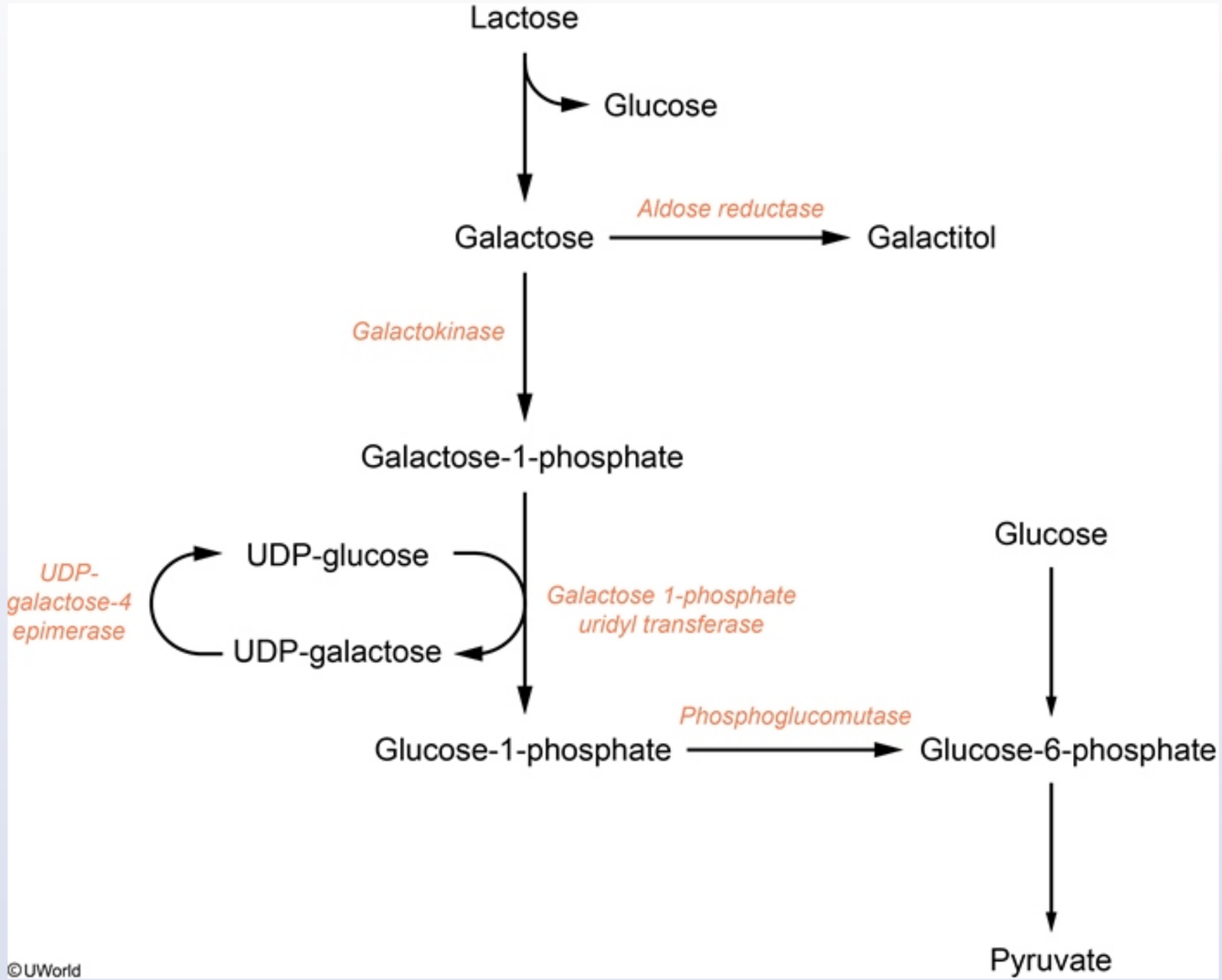
05/24/2020
Last Updated

Explanation

Lactose



Galactosemia results from deficiency of enzymes involved in galactose metabolism. First, lactose is broken down to galactose and glucose.

Galactosemia results from deficiency of enzymes involved in galactose metabolism. First, lactose is broken down to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme **galactokinase** (GALK). GALK deficiency causes galactose buildup and this excess is converted to **galactitol**, an osmotic agent that causes **cataracts**. Excess galactose also spills into the urine and causes it to test positive for a reducing substance. Serious systemic manifestations are not seen in GALK deficiency, and cataracts may be the only manifestation.

In contrast, deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) results in a more serious form of galactosemia. This is related to the accumulation of galactose-1-phosphate, a toxic metabolite that causes hepatic and renal dysfunction. Consequently, patients with GALT deficiency present early, in the neonatal period, with vomiting, lethargy, and failure to thrive.

This patient's late presentation, normal growth, and the isolated presence of cataract are indicative of GALK deficiency. Infants born in the United States undergo **routine newborn screens** for detecting inborn errors of metabolism, such as galactosemia.

(Choice A) Patients with aldolase B deficiency (hereditary fructose intolerance) cannot metabolize fructose and develop hypoglycemia, hypophosphatemia, and failure to thrive. Although reducing substances can be positive in the urine, cataracts are not present.

(Choice B) Alpha-galactosidase A deficiency (X-linked recessive) results in Fabry disease, which can present with cataracts. However, neurological findings (eg, numbness, tingling, burning pain in the hands and feet) and angiokeratomas are also characteristic.

(Choice C) Fructokinase deficiency leads to essential fructosuria, a benign condition that can result in a positive test for reducing substance but not cataracts.

(Choice E) Glucose-6-phosphatase converts glucose-6-phosphate to glucose. Deficiency of glucose-6-phosphatase causes glycogen storage disease type 1 (von Gierke disease). The main clinical manifestations are hypoglycemia, lactic acidosis, hepatomegaly, and hypertriglyceridemia. Cataracts are not seen.

(Choice F) Tay-Sachs disease results from hexosaminidase A deficiency. Affected infants have retinal cherry-red spots and loss of motor skills. Cataracts are not seen.

(Choice G) Sphingomyelinase deficiency is seen in Niemann-Pick disease and leads to accumulation of sphingomyelin. Characteristics include hepatosplenomegaly, motor neuropathy, anemia, and macular cherry-red spots but not cataracts.

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(Choice G) Sphingomyelinase deficiency is seen in Niemann-Pick disease and leads to accumulation of sphingomyelin. Characteristics include hepatosplenomegaly, motor neuropathy, anemia, and macular cherry-red spots but not cataracts.

Educational objective:
Lenticular accumulation of galactitol in the lenses of patients with galactosemia can cause osmotic damage and development of cataracts. Cataracts may be the only manifestation of galactokinase deficiency.

References

- Early cataract formation due to galactokinase deficiency: impact of newborn screening.

Biochemistry	Gastrointestinal & Nutrition	Galactosemia
Subject	System	Topic

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(Choice A) Patients with aldolase B deficiency (hereditary fructose intolerance) cannot metabolize fructose and develop hypoglycemia

Exhibit Display

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A 64-year-old man comes to the emergency department due to severe abdominal pain, nausea, and vomiting. He has a history of hypertension, myocardial infarction, and systolic heart failure. His blood pressure is 100/60 mm Hg, pulse is 116/min and irregular, and respirations are 24/min. Examination shows a soft, mildly distended, and tender abdomen. Laboratory results are as follows:

Serum chemistry		
Sodium	136 mEq/L	
Chloride	96 mEq/L	
Bicarbonate	12 mEq/L	
Arterial blood gases		
pH	7.20	
$PaCO_2$	26 mm Hg	
Lactic acid	6.2 mmol/L	(normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

- A. Enolase
- B. Lactate dehydrogenase
- C. Pyruvate carboxylase
- D. Pyruvate dehydrogenase

Sodium	136 mEq/L
Chloride	96 mEq/L
Bicarbonate	12 mEq/L

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- B. Lactate dehydrogenase
- C. Pyruvate carboxylase
- D. Pyruvate dehydrogenase
- E. Pyruvate kinase

Submit

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Arterial blood gases

pH	7.20
$PaCO_2$	26 mm Hg

Lactic acid	6.2 mmol/L	(normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

A. Enolase (1%)
B. Lactate dehydrogenase (25%)
C. Pyruvate carboxylase (8%)
✓ D. Pyruvate dehydrogenase (57%)
E. Pyruvate kinase (7%)

Omitted
Correct answer

57%
Answered correctly

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Time Spent

02/18/2020
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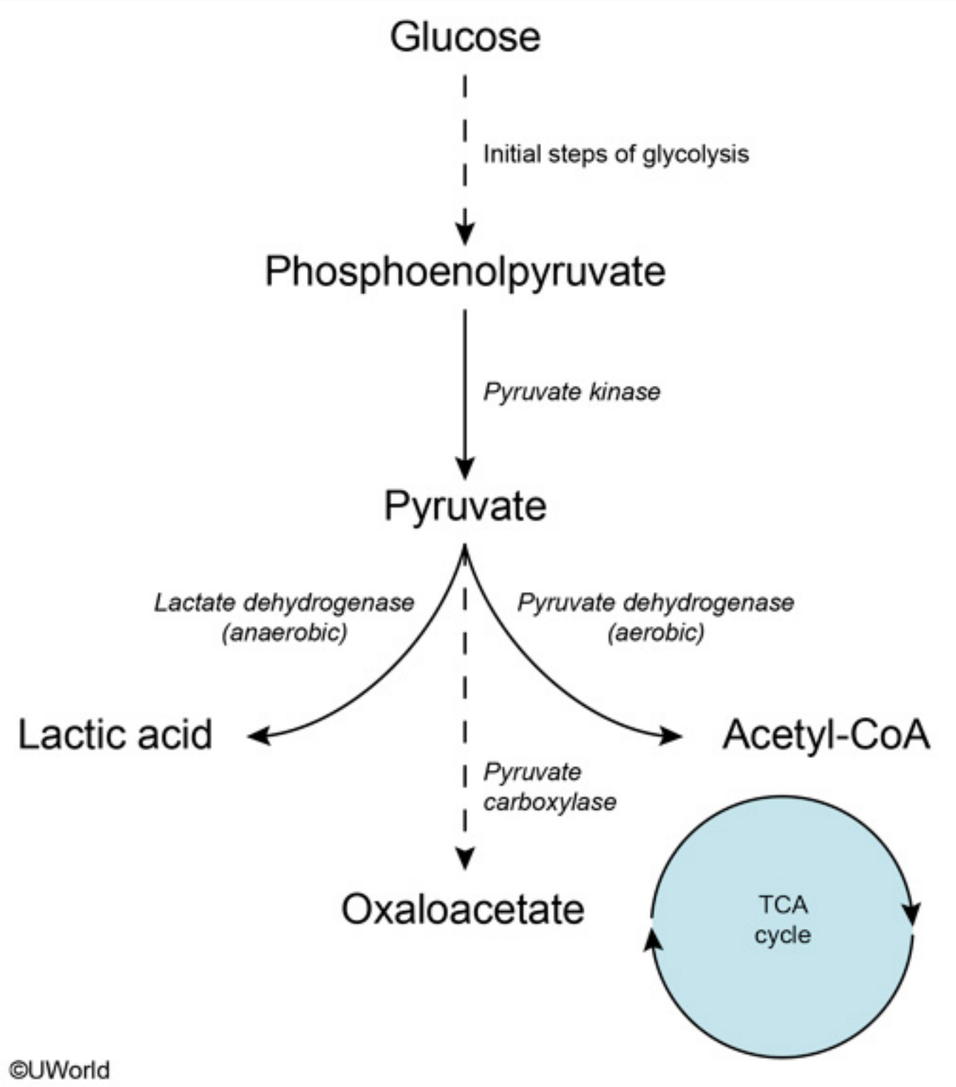

This patient has **acute mesenteric ischemia**, with inadequate delivery of oxygen to intestinal tissues. During glycolysis, the concentration of

This patient has **acute mesenteric ischemia**, with inadequate delivery of oxygen to intestinal tissues. During glycolysis, the concentration of oxygen in the tissues affects the metabolic fate of pyruvate. In the presence of oxygen, pyruvate is preferentially converted to acetyl coenzyme A by pyruvate dehydrogenase in the mitochondrial matrix. Acetyl coenzyme A then undergoes oxidation in the citric acid (TCA) cycle. However, under **hypoxic conditions**, intracellular accumulation of NADH **inhibits pyruvate dehydrogenase**. As a result, increased amounts of **pyruvate** are converted to **lactate** by lactate dehydrogenase **(Choice B)**, which regenerates NAD^+ from NADH (allowing for limited ATP production via anaerobic glycolysis). With significant tissue ischemia, lactate begins to accumulate in the circulation and can lead to **lactic acidosis**. Patients with lactic (or other metabolic) acidosis will typically hyperventilate to eliminate CO_2 and induce a compensatory respiratory alkalosis.

(Choices A and E) 2-phosphoglycerate is converted to phosphoenolpyruvate by the enzyme enolase. Phosphoenolpyruvate is subsequently metabolized to pyruvate by pyruvate kinase. These reactions are performed under both aerobic and anaerobic conditions.

(Choice C) Pyruvate can also be converted to oxaloacetate by pyruvate carboxylase. This enzyme is involved in regeneration of glucose from pyruvate by the process of gluconeogenesis.

Educational objective:

In the presence of oxygen, pyruvate produced during glycolysis is converted by pyruvate dehydrogenase to acetyl coenzyme A, which is subsequently metabolized by oxidative phosphorylation. However, if inadequate oxygen is present in the tissues, pyruvate is converted to lactate by lactate dehydrogenase, leading to lactic acidosis.

References

- Clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department.

Biochemistry	General Principles	Metabolic acidosis
Subject	System	Topic

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A 3-year-old boy who recently immigrated to the United States is brought to the physician by his parents because he has not yet begun to walk or speak. Assessment of his developmental milestones shows severe intellectual disability. He dies 6 months later from refractory seizures resulting in respiratory failure. Autopsy shows pallor of the substantia nigra, locus ceruleus, and vagal nucleus dorsalis. The underlying condition responsible for this patient's death is most likely caused by a deficiency of which of the following enzymes?

A. Branched-chain ketoacid dehydrogenase
B. Dopamine hydroxylase
C. Homogentisic acid oxidase
D. Phenylalanine hydroxylase
E. Tyrosinase

Submit

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A. Branched-chain ketoacid dehydrogenase (6%)
B. Dopamine hydroxylase (23%)
C. Homogentisic acid oxidase (4%)
✓ D. Phenylalanine hydroxylase (50%)
E. Tyrosinase (15%)

Omitted
Correct answer
D

50%
Answered correctly

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Time Spent

03/12/2020
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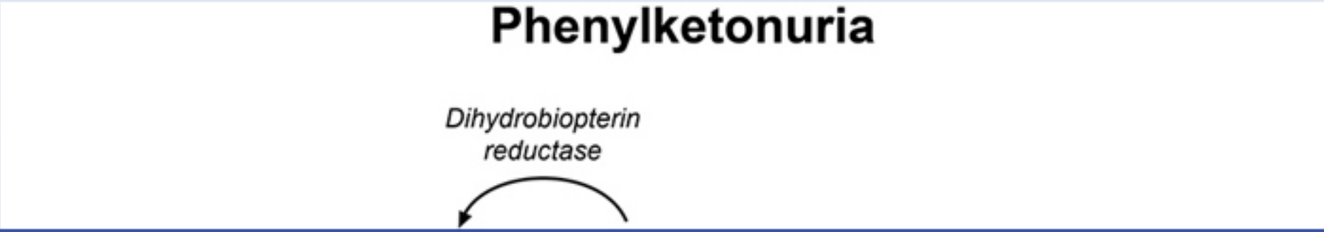
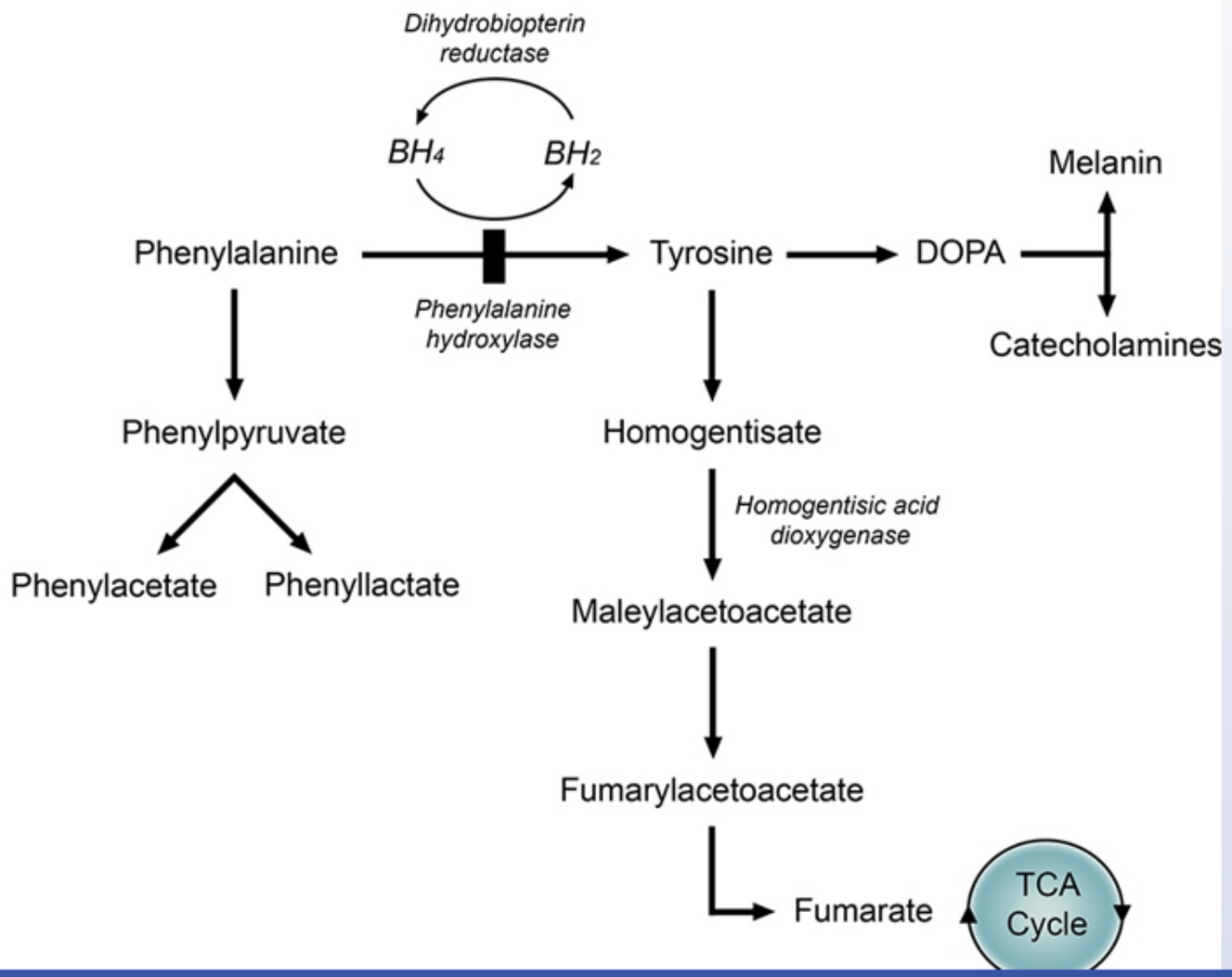
Explanation



Phenylketonuria



This patient's severe intellectual disability, history of seizures, and abnormal pallor of catecholaminergic brain nuclei on autopsy are suggestive of phenylketonuria (PKU). PKU results from the inability to convert phenylalanine into tyrosine, a reaction which is normally catalyzed by phenylalanine hydroxylase. This enzyme requires the cofactor tetrahydrobiopterin (BH_4), which is regenerated from dihydrobiopterin (BH_2) by the enzyme dihydropteridine reductase. Although neonatal hyperphenylalaninemia can be caused by deficiency of either enzyme, most cases are attributable to abnormalities in phenylalanine hydroxylase.

It is believed that excess phenylalanine and the presence of large concentrations of phenylalanine metabolites (eg, phenyllactate & phenylacetate) contribute to the brain damage seen in PKU. Hypopigmentation involving the skin, hair, eyes, and catecholaminergic brain nuclei (which produce a dark pigment known as neuromelanin) results from the inhibitory effect of excess phenylalanine on melanin synthesis. The classic musty or mousy body odor is due to the accumulation of abnormal phenylalanine metabolites.

(Choice A) Branched-chain ketoacid dehydrogenase catalyzes decarboxylation of the α-ketoacid derivatives of all 3 branched chain amino acids: leucine, isoleucine, and valine. Deficiency causes maple syrup urine disease, which is characterized by a burnt-sugar smell in the urine of affected patients. Hypopigmentation is not seen in the condition.

(Choice B) Dopamine hydroxylase is the enzyme that catalyzes the biosynthesis of norepinephrine from dopamine. Deficiency of this enzyme causes a rare form of dysautonomia characterized by ptosis, orthostatic hypotension, hypoglycemia, and hypothermia.

(Choice C) Alkaptonuria is an autosomal recessive disorder of tyrosine degradation caused by a deficiency of homogentisic acid oxidase. This condition results in the accumulation of large amounts of homogentisic acid, leading to connective tissue hyperpigmentation and degenerative joint disease.

(Choice E) Albinism is an autosomal recessive disorder caused by defects in the biosynthesis and distribution of melanin. It is most commonly due to depressed or absent tyrosinase activity. Melanin synthesis begins with the conversion of tyrosine to DOPA and DOPA to dopaquinone by the enzyme tyrosinase in melanocytes. Albinism does not present with neurologic dysfunction.

Educational objective:
Deficiency of the enzyme phenylalanine hydroxylase or its cofactor tetrahydrobiopterin causes accumulation of phenylalanine in body fluids and the central nervous system. Homozygous infants are normal at birth but gradually develop severe intellectual disability and seizures if left untreated. Hypopigmentation of the skin, hair, eyes, and catecholaminergic brain nuclei is also frequently seen.

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Biochemistry	Nervous System	Phenylketonuria
Subject	System	Topic

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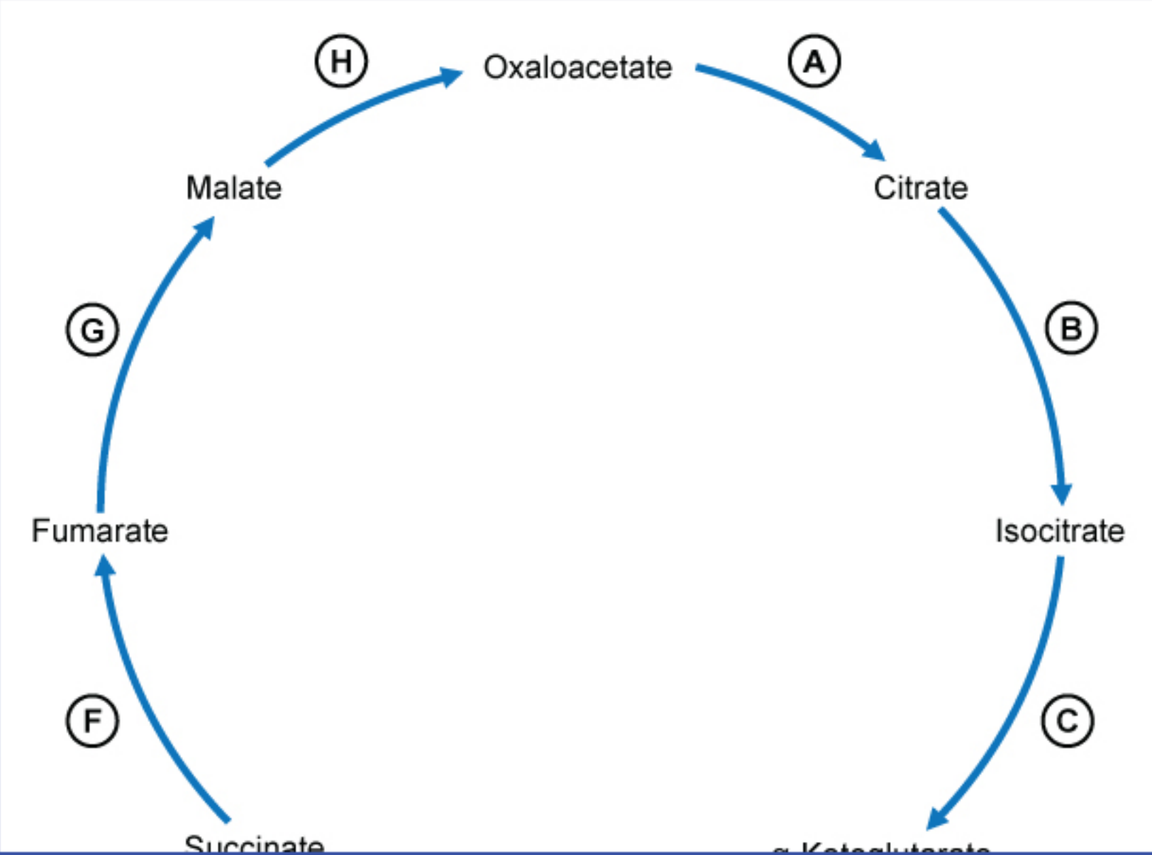
A 44-year-old homeless man is brought to the emergency department after police officers found him agitated and confused. During transport to the hospital, he is started on intravenous fluids with dextrose. On arrival, the patient is disoriented but cooperative. Physical examination shows bruises on his forehead, forearms, and shins. Extraocular findings include bilateral horizontal nystagmus and decreased lateral eye movements. He also has an unsteady gait with widely-spaced legs and short steps. The ambulance personnel state that the patient's extraocular movements were intact when they picked him up. A review of the medical record shows that the patient has been admitted to the hospital with alcohol intoxication several times before. Which of the following reactions is likely to be the most impaired in this patient?



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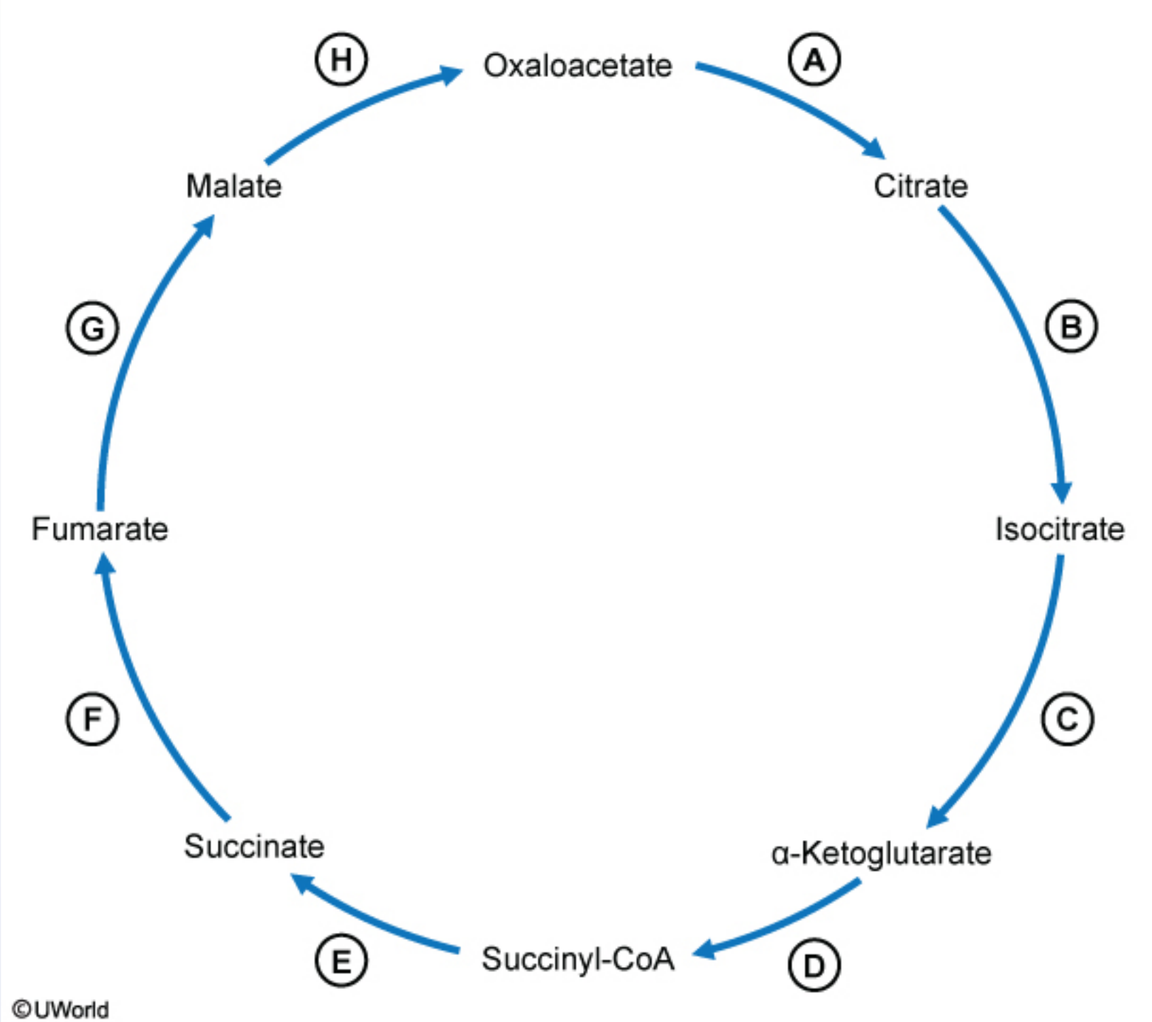

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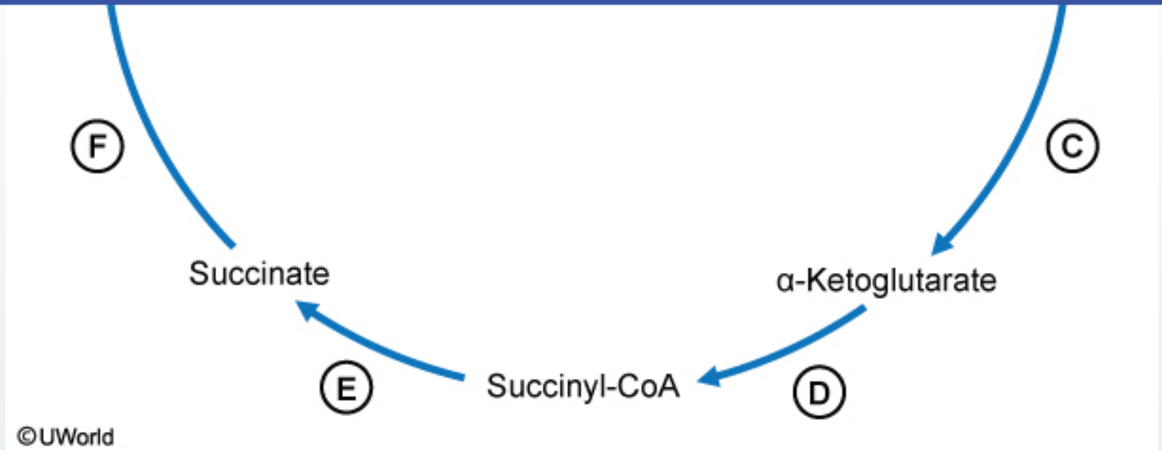

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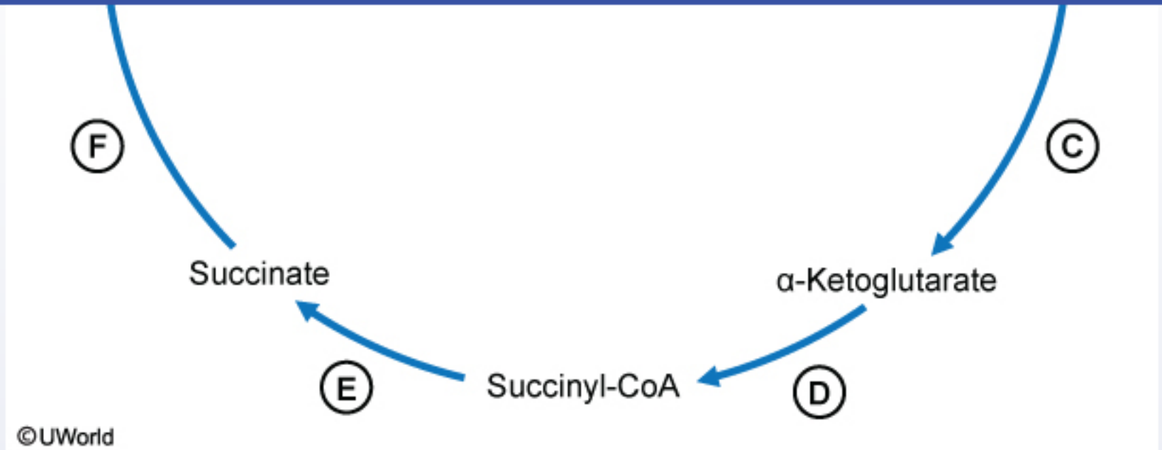

- A. A (8%)
- B. B (2%)
- C. C (14%)
- ✓ D. D (51%)
- E. E (7%)
- F. F (3%)
- G. G (2%)
- H. H (9%)

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Correct answer

51%
Answered correctly

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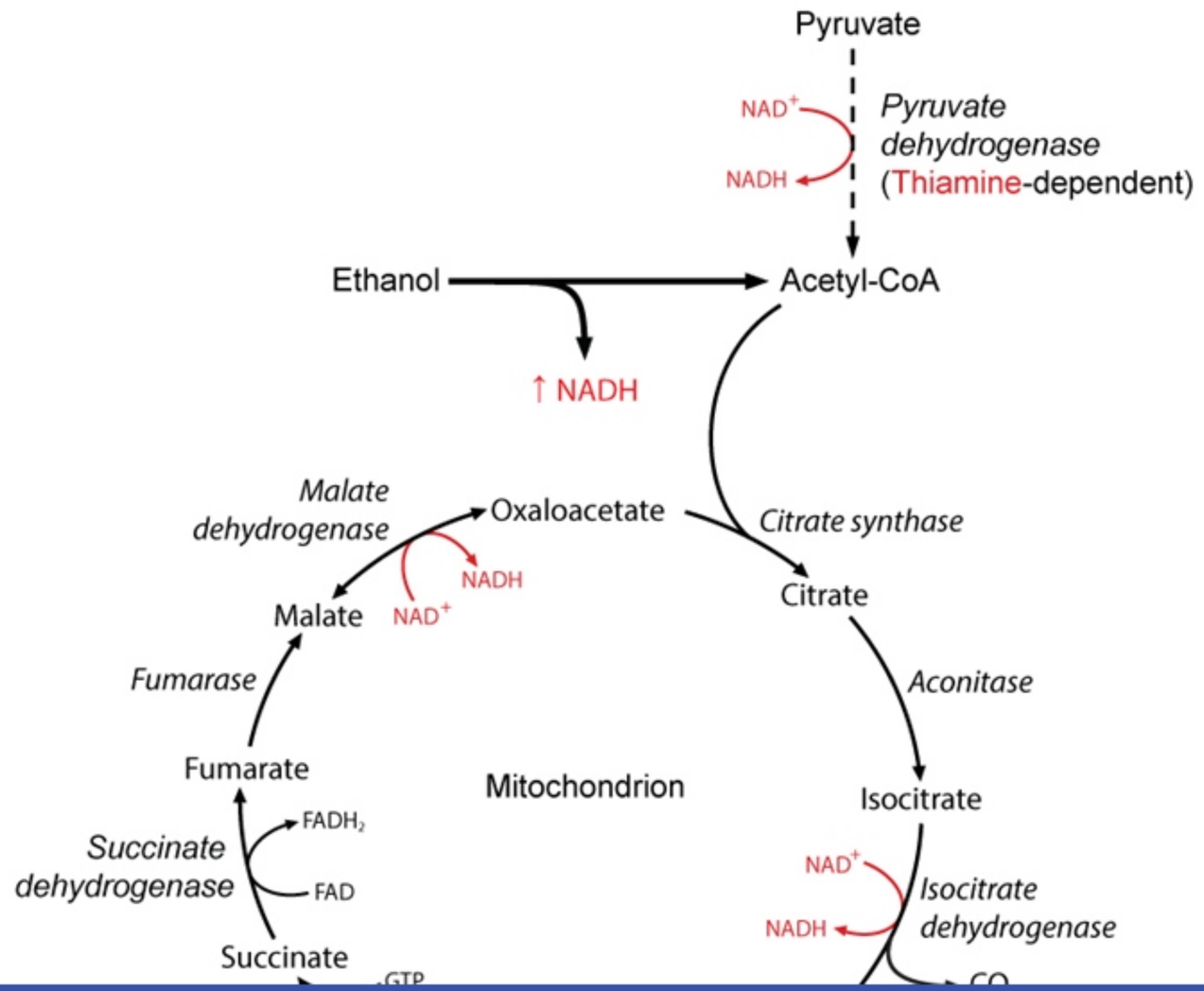
Inhibition of the citric acid cycle by ethanol



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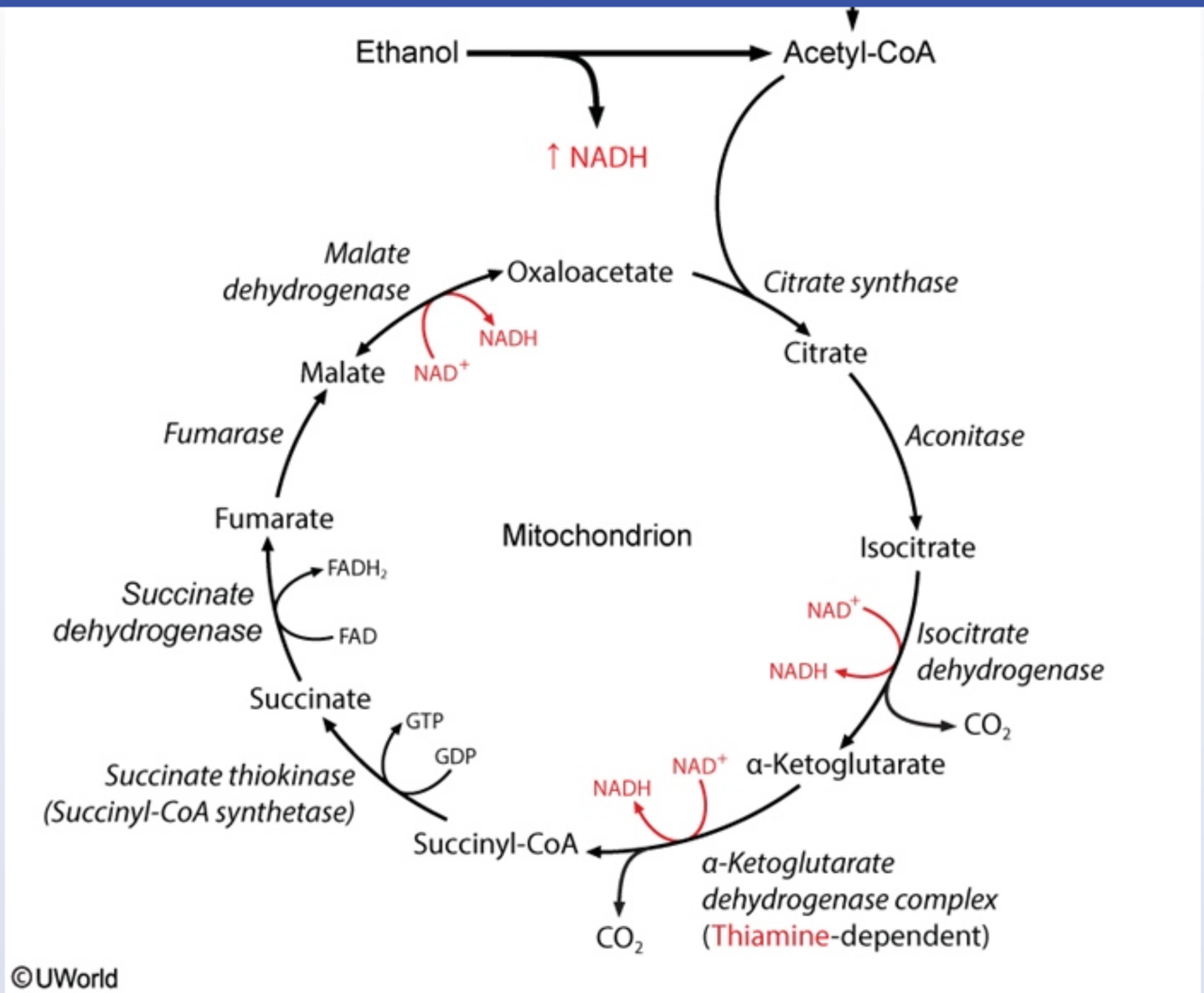

Patients with **chronic alcoholism** are frequently deficient in **thiamine**, a necessary cofactor for **pyruvate dehydrogenase, α-ketoglutarate**

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Patients with **chronic alcoholism** are frequently deficient in **thiamine**, a necessary cofactor for **pyruvate dehydrogenase, α-ketoglutarate dehydrogenase**, and transketolase. Administration of glucose to thiamine-deficient patients can cause rapid depletion of the small amount of thiamine remaining in the circulation. This can result in neuronal injury within highly metabolic brain regions, leading to acute Wernicke encephalopathy.

The metabolism of ethanol by alcohol dehydrogenase and aldehyde dehydrogenase consumes NAD^+ and increases the **NADH to NAD^+ ratio**. This skewed ratio inhibits all pathways requiring NAD^+; as a result, the entire **citric acid cycle is inhibited**. However, in the setting of Wernicke encephalopathy, **thiamine-dependent** enzymes are **especially affected** due to the lack of NAD^+ and thiamine.

(Choice A) Even though pyruvate dehydrogenase is markedly inhibited by high NADH and lack of thiamine, acetyl-CoA still accumulates intracellularly because *ethanol itself* is metabolized to acetyl-CoA. Thus, citrate synthase is not inhibited more than the other non-thiamine-requiring TCA cycle enzymes.

(Choices C and H) α-ketoglutarate, isocitrate, and malate dehydrogenase all require NAD^+ and will be inhibited during ethanol intoxication due to depletion of this substrate. However, of these enzymes, only α-ketoglutarate dehydrogenase also requires thiamine as a cofactor.

Educational objective:
Pyruvate dehydrogenase and α-ketoglutarate dehydrogenase require thiamine as a cofactor. Administration of glucose to thiamine-deficient patients (eg, alcoholics) can result in Wernicke encephalopathy (eg, acute confusion, ophthalmoplegia, and ataxia) due to increased thiamine demand.

References

- Thiamine pyrophosphate-requiring enzymes are altered during pyrithiamine-induced thiamine deficiency in cultured human lymphoblasts.
- Dietary thiamin level influences levels of its diphosphate form and thiamin-dependent enzymic activities of rat liver.

Biochemistry	Psychiatric/Behavioral & Substance Abuse	Wernicke korsakoff syndrome
Subject	System	Topic

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Educational objective:
Pyruvate dehydrogenase
patients (eg, alcoholics) ca
demand.

References

- Thiamine pyrophospha
- Dietary thiamin level in

Biochemistry
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Exhibit Display

Wernicke encephalopathy	
Associated conditions	• Chronic alcoholism (most common) • Malnutrition (eg, anorexia nervosa) • Hyperemesis gravidarum
Pathophysiology	• Thiamine deficiency
Clinical features	• **Encephalopathy** • **Oculomotor dysfunction** (eg, horizontal nystagmus, bilateral abducens palsy) • Postural & gait **ataxia**
Treatment	• Intravenous thiamine followed by glucose infusion

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A 7-day-old neonate born to a 28-year-old woman is brought to the office due to progressive lethargy, vomiting, and poor feeding. The mother reports an uneventful pregnancy and perinatal course. She exclusively breastfeeds the infant and has no medical problems in any of her other children. On examination, the infant is somnolent and dehydrated with decreased muscle tone. Laboratory studies reveal metabolic acidosis with an elevated anion gap, ketosis, and hypoglycemia. Further evaluation reveals a markedly elevated propionic acid level due to defective conversion of propionyl-CoA to methylmalonyl-CoA. This patient is most likely unable to use which of the following amino acids for energy production?

- A. Alanine
- B. Aspartate
- C. Glutamate
- D. Lysine
- E. Phenylalanine
- F. Valine

Submit

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- A. Alanine (16%)
- B. Aspartate (9%)
- C. Glutamate (10%)
- D. Lysine (13%)
- E. Phenylalanine (15%)
- ✓ F. Valine (33%)

Omitted
Correct answer
F

33%
Answered correctly

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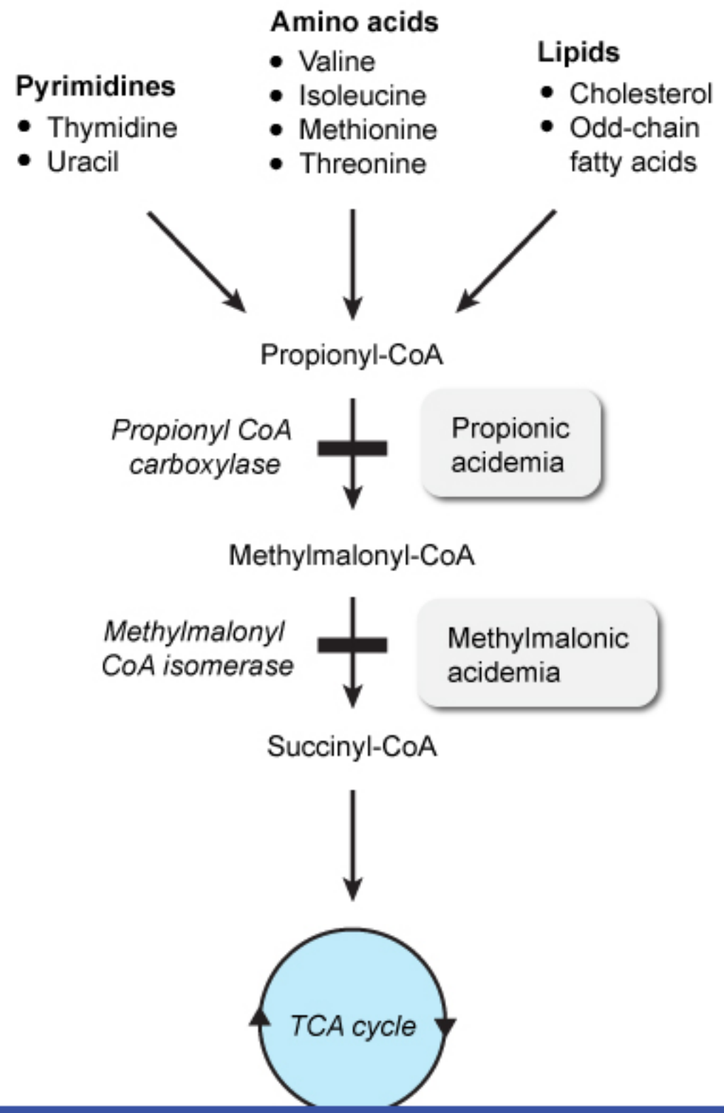
04/07/2020
Last Updated

Explanation

Organic acidemia

Organic acidemia



Catabolism of several essential amino acids (**valine**, **isoleucine**, **methionine**, and **threonine**) along with **odd-chain fatty acids** results in the generation of propionyl-CoA. Propionyl-CoA is subsequently converted to methylmalonyl-CoA in a reaction catalyzed by biotin-dependent propionyl-CoA carboxylase. Isomerization of methylmalonyl-CoA then generates succinyl-CoA, which enters the TCA cycle.

This patient's presentation is consistent with **propionic acidemia**, an autosomal recessive organic acidemia caused by congenital deficiency of propionyl-CoA carboxylase. This enzyme catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. In its absence, excess propionic acid accumulates in the bloodstream, causing **severe metabolic acidosis**. Hypoglycemia and ketosis frequently develop secondary to the acidosis. Affected patients present 1-2 weeks after birth with lethargy, poor feeding, vomiting, and hypotonia. Treatment involves starting a low-protein diet containing minimal amounts of valine, isoleucine, methionine, and threonine.

(Choice A) Alanine transaminase catalyzes the transfer of an amino group from alanine to α-ketoglutarate, generating pyruvate that can be used for gluconeogenesis.

(Choice B) Aspartate is a nonessential amino acid; it can be converted into oxaloacetate for use in the TCA cycle by aspartate transaminase.

(Choice C) Glutamate is deaminated by glutamate dehydrogenase to form the TCA cycle intermediate α-ketoglutarate.

(Choice D) Lysine and leucine are essential amino acids that are strictly ketogenic. They are metabolized into acetyl-CoA, which is a precursor for ketone bodies.

(Choice E) Phenylalanine is converted to tyrosine by the enzyme phenylalanine hydroxylase. Tyrosine is further converted into fumarate (TCA cycle intermediate) and acetoacetate (ketone body).

Educational objective:
Propionyl-CoA is derived from the metabolism of valine, isoleucine, methionine, threonine, and odd-chain fatty acids. Congenital deficiency of propionyl-CoA carboxylase, the enzyme responsible for the conversion of propionyl-CoA to methylmalonyl-CoA, leads to the development of propionic acidemia. The condition presents with lethargy, poor feeding, vomiting, and hypotonia 1-2 weeks after birth.

Biochemistry	Nervous System	Organic acidemias
Subject	System	Topic

An 8-month-old girl is brought to the office for evaluation of irritability and regression of motor skills. Her birth was unremarkable and she appeared to develop normally, but she can no longer sit or roll over. Her parents have also noticed that she startles easily with loud noises. Head circumference measurement is consistent with macrocephaly. Bilateral funduscopic evaluation shows a bright red fovea centralis that is surrounded by a contrasting white macula. Peripheral vision is decreased. Abdominal examination is normal. Accumulation of which of the following metabolites is most likely present in this patient's tissues?

A. Galactocerebroside
B. Globotriaosylceramide
C. Glucocerebroside
D. Glycogen
E. GM_2 ganglioside
F. Heparan sulfate
G. Sphingomyelin

Submit

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- A. Galactocerebroside (11%)
- B. Globotriaosylceramide (1%)
- C. Glucocerebroside (9%)
- D. Glycogen (1%)
- ✓ E. GM_2 ganglioside (56%)
- F. Heparan sulfate (2%)
- G. Sphingomyelin (17%)

Omitted
Correct answer
E

56%
Answered correctly

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Explanation

Sphingolipidoses

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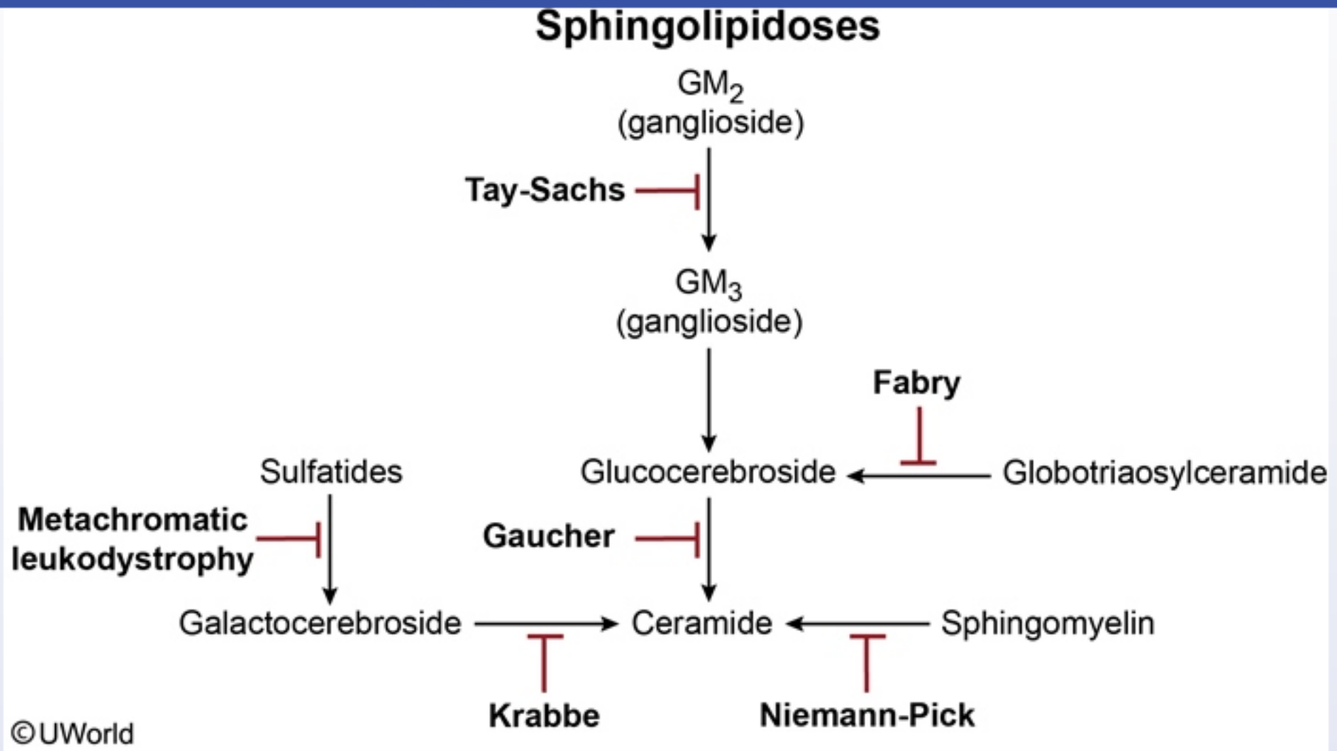

Tay-Sachs disease is an autosomal recessive neurodegenerative disorder commonly seen in the Ashkenazi Jewish population. Tay-Sachs is caused by β-hexosaminidase A deficiency, which results in accumulation of the cell membrane glycolipid **GM2 ganglioside** within lysosomes.

Affected infants typically have normal development in the first few months of life, followed by progressive **neurologic deterioration** as glycolipids accumulate in the brain. Clinical consequences include weakness, hypotonia, developmental regression, seizures, blindness, and spasticity. Physical examination shows macrocephaly and an abnormal startle reflex with acoustic stimuli. In addition, the center of the fovea (blue arrow) appears bright red (**cherry-red macula spot**) as it is surrounded by white macula appearing as a halo. The halo results from a loss of retinal transparency due to ganglioside buildup in ganglion cells. The center of the fovea lacks ganglion cells, so the underlying choroid transmits its red color. Patients usually die by age 2-5 years.

(Choice A) Like Tay-Sachs, Krabbe disease (galactocerebroside accumulation) causes progressive neurodegeneration. However, patients with

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(Choice A) Like Tay Sachs, Krabbe disease (galactocerebroside accumulation) causes progressive neurodegeneration. However, patients with Krabbe disease also have peripheral neuropathy and optic atrophy.

(Choice B) Fabry disease (globotriaosylceramide accumulation) causes angiokeratomas, peripheral neuropathy, and glomerulopathy that typically present in adulthood.

(Choices C and G) A similar cherry-red spot occurs in other lysosomal enzyme deficiencies, such as Gaucher disease and Niemann-Pick disease. Gaucher disease (β-glucocerebroside accumulation) and Niemann-Pick disease (sphingomyelin accumulation) are both unlikely due to this patient's normal abdominal examination (eg, no hepatosplenomegaly).

(Choice D) Glycogen storage diseases include von Gierke disease and Pompe disease. Infants with von Gierke disease (glucose-6-phosphatase deficiency) typically have hepatomegaly, hypoglycemia, seizures, and/or lactic acidosis. Pompe disease (lysosomal α-1,4-glucosidase deficiency) classically causes cardiomegaly and severe hypotonia.

(Choice F) Mucopolysaccharidosis (eg, Hurler syndrome, Hunter syndrome) are lysosomal storage disorders that cause buildup of glycosaminoglycans (GAGs) such as heparan and dermatan sulfate. GAG accumulation causes neurocognitive decline as well as coarse facial features and skeletal abnormalities.

Educational objective:
Tay-Sachs disease is an autosomal recessive disorder caused by β-hexosaminidase A deficiency, which results in GM_2 ganglioside accumulation. Key clinical features include progressive neurodegeneration and a cherry-red macular spot. In contrast to patients with Niemann-Pick disease,

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Educational objective:
Tay-Sachs disease is an autosomal recessive disorder caused by β-hexosaminidase A deficiency, which results in GM_2 ganglioside accumulation. Key clinical features include progressive neurodegeneration and a cherry-red macular spot. In contrast to patients with Niemann-Pick disease, those with Tay Sachs disease have no hepatosplenomegaly.

References

- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly.
- Gangliosidoses

Biochemistry	Nervous System	Tay sachs
Subject	System	Topic

An 18-month-old boy is brought to the office due to language regression. He said several words at his 1-year appointment but now no longer speaks any words at all. His moods have also become more unpredictable over the past 4 months with frequent tantrums. The parents tried to bring him in sooner for evaluation, but they live in an impoverished part of the city and experienced financial difficulties with transportation to the office. On physical examination, the boy is quiet and maintains appropriate eye contact throughout the visit. Hemoglobin is 9 g/dL. Which of the following enzymes is most likely inhibited in this patient?

- A. δ-Aminolevulinate dehydratase
- B. Bilirubin glucuronyl transferase
- C. Porphobilinogen deaminase
- D. Pyruvate kinase
- E. Uroporphyrinogen decarboxylase

Submit

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- ✓ A. δ-Aminolevulinate dehydratase (61%)
- B. Bilirubin glucuronyl transferase (5%)
- C. Porphobilinogen deaminase (15%)
- D. Pyruvate kinase (7%)
- E. Uroporphyrinogen decarboxylase (9%)

Omitted
Correct answer
A

61%
Answered correctly

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Time Spent

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Last Updated

Explanation

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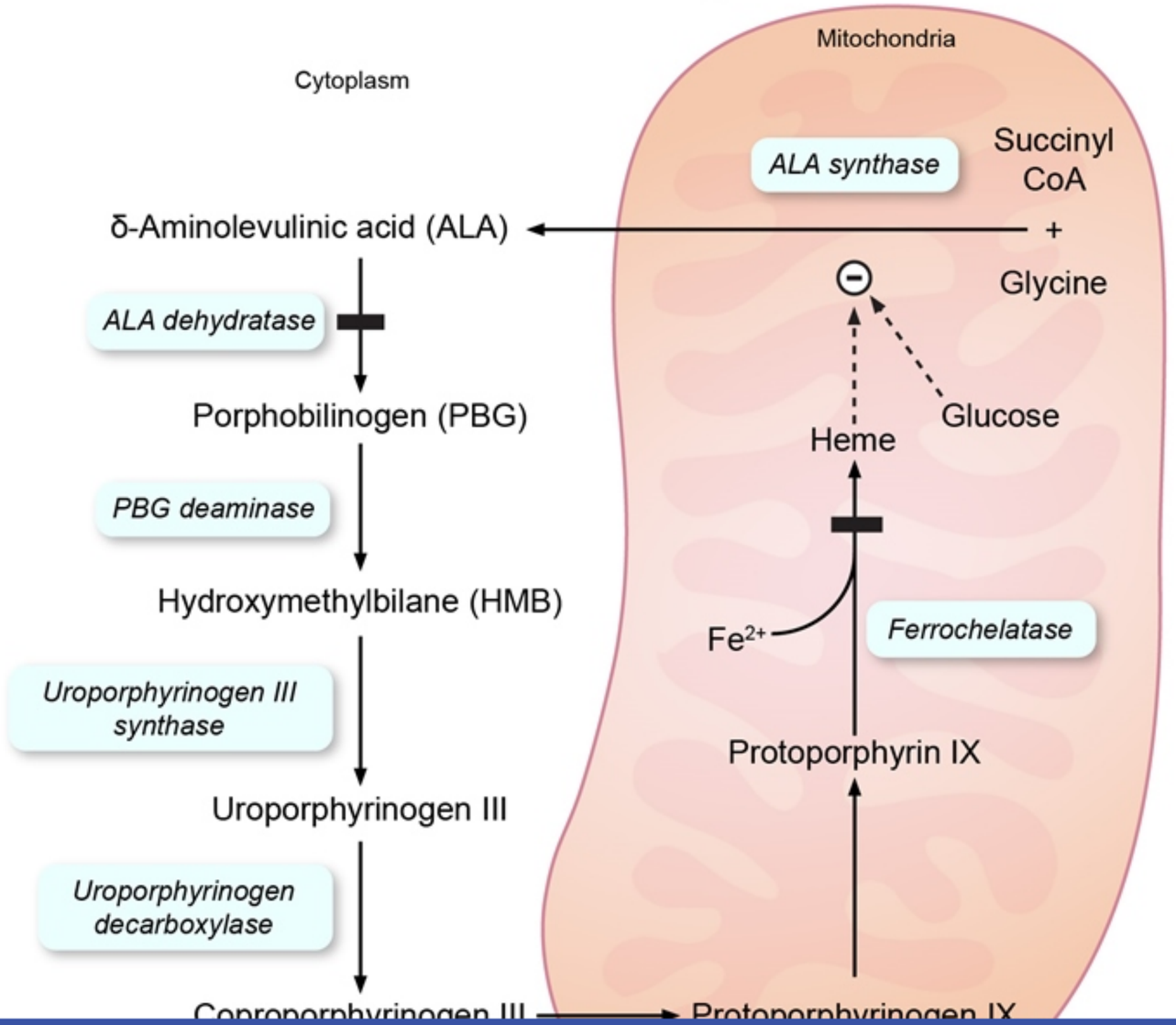
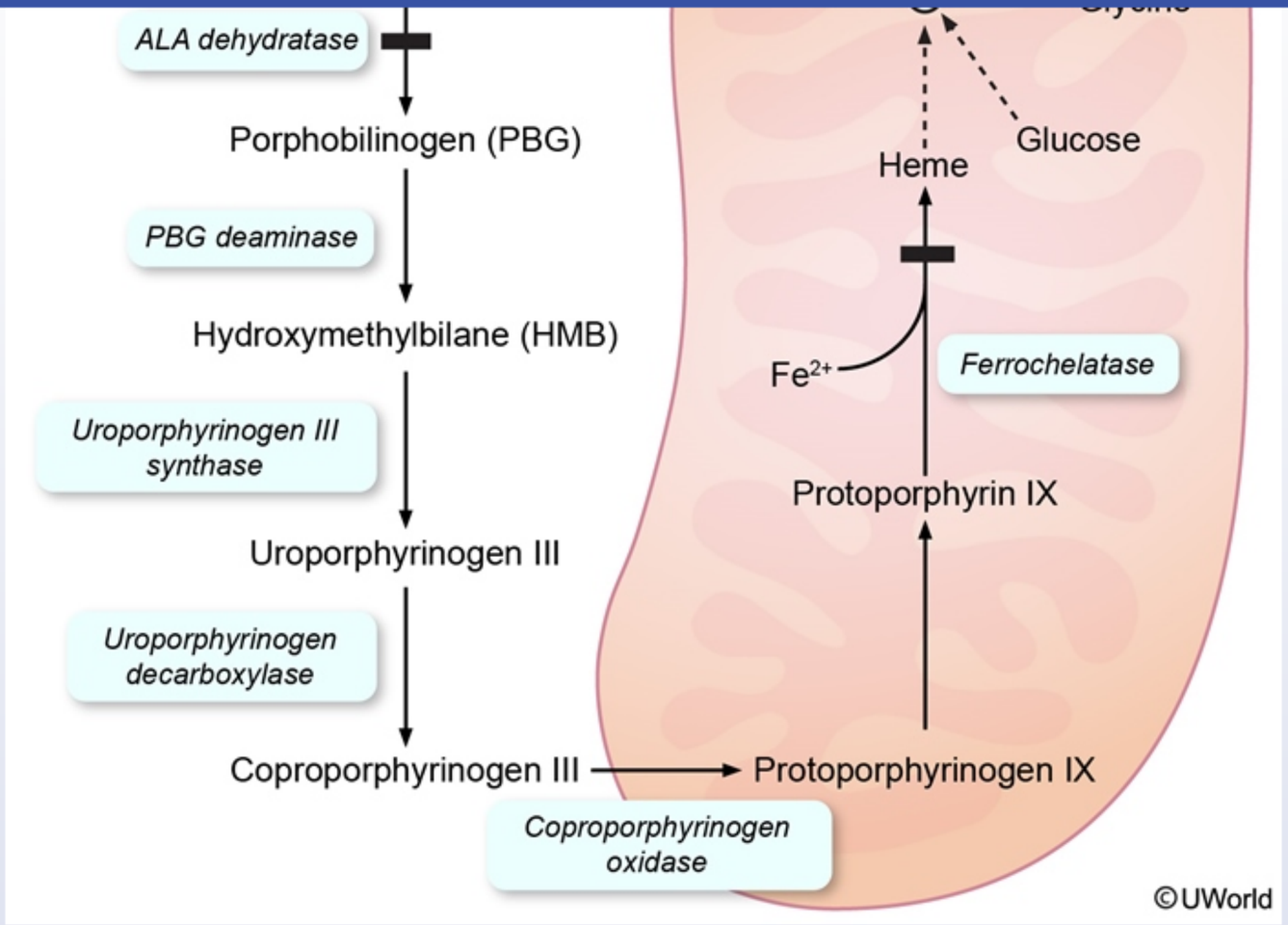
Lead toxicity





This child's language regression and anemia are most likely due to lead poisoning. **Lead toxicity** is most prevalent among **impoverished children** residing in deteriorating urban **housing built before 1978**. Young children are particularly susceptible to lead poisoning via inhalation and ingestion of lead-based paint dust or chips due to normal crawling and mouthing behaviors. The incomplete blood-brain-barrier in children is vulnerable to the **neurotoxic** effects of lead, which include long-standing behavioral problems and developmental delay or regression.

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Anemia in lead poisoning results from inhibition of **ferrochelatase** and **δ-aminolevulinic acid (ALA) dehydratase** in the heme biosynthesis pathway. Because protoporphyrin IX cannot combine with iron (Fe^{2+}) to form heme due to ferrochelatase inhibition, it instead incorporates a zinc ion, leading to **elevated zinc protoporphyrin levels**. In addition, ALA levels are increased. Lead poisoning also commonly coexists with iron deficiency anemia, and severe lead poisoning can also induce hemolytic anemia.

(Choice B) Glucuronyl transferase (uridine 5'-diphospho-glucuronosyltransferase) is necessary for hepatic bilirubin conjugation. Gilbert syndrome, a condition marked by jaundice (elevated unconjugated bilirubin levels) during times of stress, results from mutations in the gene encoding glucuronyl transferase.

(Choice C) Defects in porphobilinogen deaminase result in acute intermittent porphyria (AIP), a disorder characterized by acute attacks of abdominal pain, neuropsychiatric symptoms, and red or brown urine. The chronicity of symptoms, lack of abdominal pain, and anemia make AIP unlikely in this patient.

(Choice D) Pyruvate kinase deficiency is typically inherited in an autosomal recessive pattern and leads to hemolytic anemia. Pyruvate kinase deficiency can present with pallor, scleral icterus, and splenomegaly, but it does not present with behavioral regression or language difficulties.

(Choice E) Defects in uroporphyrinogen decarboxylase cause porphyria cutanea tarda (PCT), the most common form of porphyria. Patients with PCT exhibit chronic photosensitivity with blistering in areas of sun exposure and elevated levels of uroporphyrinogen in the urine.

Educational objective:
Young children who reside in homes built before 1978 are at significant risk for lead toxicity. Lead directly inhibits ferrochelatase and δ-aminolevulinic acid (ALA) dehydratase, resulting in anemia, ALA accumulation, and elevated zinc protoporphyrin levels. Neurotoxicity is also a significant long-term complication.

References

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References

- Lead toxicity, a review of the literature. Part 1: Exposure, evaluation, and treatment.
- A study on the ALAD gene polymorphisms associated with lead exposure.
- The important health impact of where a child lives: neighborhood characteristics and the burden of lead poisoning.

Exhibit Display

Acute intermittent porphyria

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Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

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(Choice B) Glucuronyl transferase (uridine 5' diphospho glucuronosyltransferase) is necessary for hepatic bilirubin conjugation. Gilbert

Exhibit Display

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A 68-year-old man comes to the emergency department due to abdominal pain and nausea for the past 2 days. He has a history of atherosclerotic cardiovascular disease and underwent coronary artery bypass surgery 2 years ago. Blood pressure is 105/65 mm Hg and heart rate is 120/min and irregular. Abdominal examination reveals mild diffuse tenderness and decreased bowel sounds. Laboratory studies are as follows:

Serum chemistry	
Sodium	142 mEq/L
Chloride	104 mEq/L
Bicarbonate	12 mEq/L
Creatinine	0.8 mg/dL
Arterial blood gases	
pH	7.25
$PaCO_2$	29 mm Hg
Lactic acid, venous blood	5.6 mmol/L (normal: 0.5 - 2.0 mmol/L)

ECG shows absent P waves and an irregular rate and rhythm. CT scan of the abdomen reveals colonic wall thickening and no enhancement with intravenous contrast. Urinalysis shows acidic urine. Renal metabolism of which of the following amino acids is most important for maximizing acid excretion in this patient?

A. Alanine
B. Arginine
C. Aspartate

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Chloride	104 mEq/L
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A. Alanine
B. Arginine
C. Aspartate
D. Glutamine
E. Histidine

Submit

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A. Alanine (10%)
B. Arginine (22%)
C. Aspartate (22%)
✓ D. Glutamine (36%)
E. Histidine (6%)

Omitted
Correct answer

36%
Answered correctly

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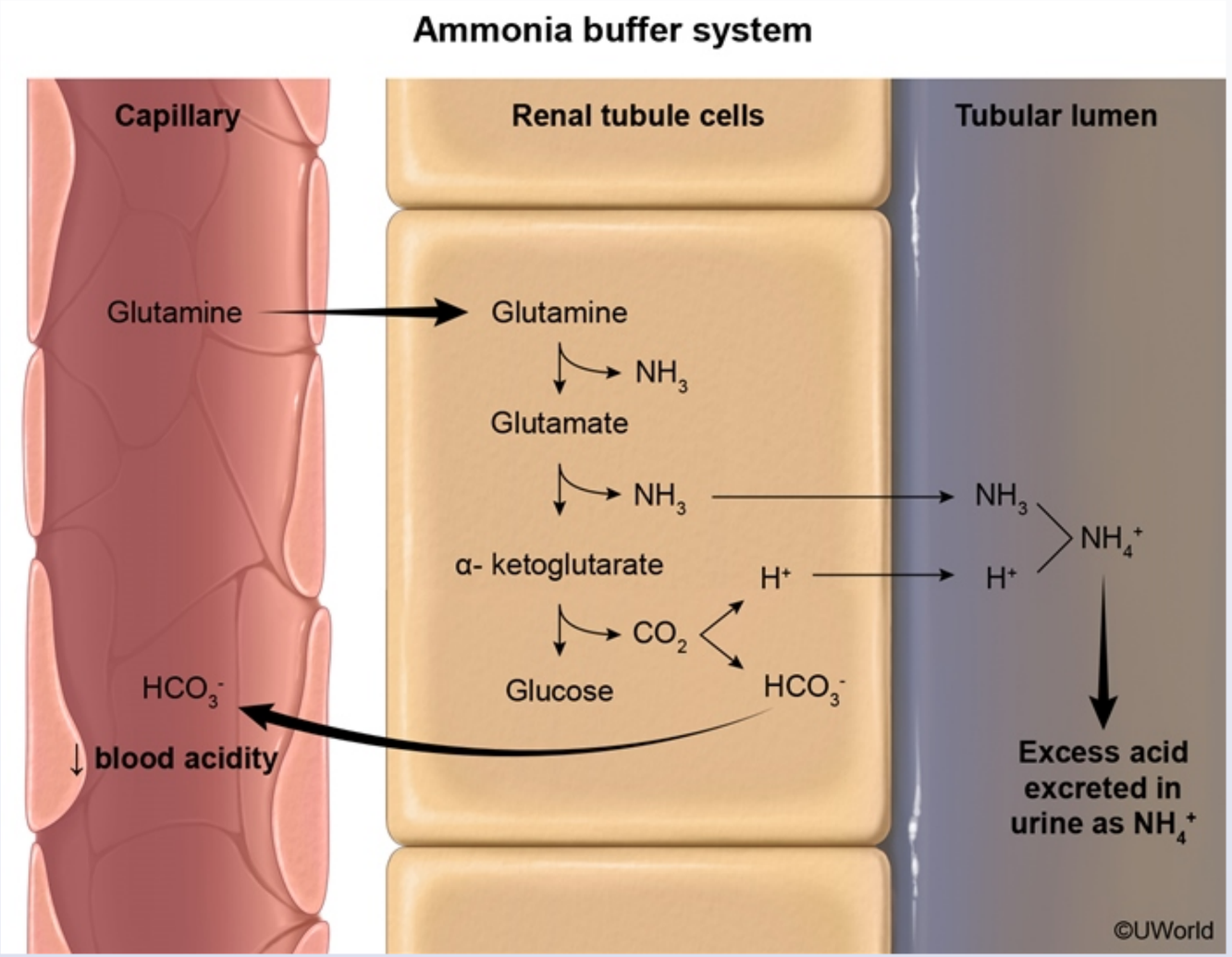

This patient has **acute ischemic colitis**, which is most likely due to embolic disease related to his atrial fibrillation. The ischemic bowel undergoes anaerobic metabolism, causing **lactate accumulation** in the blood that leads to an anion gap metabolic acidosis. Acidosis stimulates **renal ammoniagenesis**, a process by which renal epithelial cells metabolize **glutamine**, generating ammonium and bicarbonate. Ammonium

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Under normal physiologic conditions, about half of the total amount of acid secreted in the urine is in the form of ammonium, and the remainder is excreted primarily as titratable acids, particularly inorganic phosphate. However, **increased ammonium production** is almost entirely responsible for the increase in renal acid excretion seen with **chronic acidosis**.

(Choices A and C) Alanine and aspartate are glucogenic amino acids. Alanine is metabolized in the liver to produce pyruvate and aspartate can be readily interconverted with oxaloacetate.

(Choice B) Arginine is a urea cycle intermediate that helps to remove nitrogenous waste products (eg, ammonium) from the blood. Hepatic metabolism of arginine results in the production of urea and ornithine.

(Choice E) Histidine, an essential amino acid, is converted to histamine by histidine decarboxylase. Histamine is involved in the acute inflammatory response and gastric acid secretion; it also functions as a neurotransmitter.

Educational objective:
Acidosis stimulates renal ammoniagenesis, a process by which renal tubular epithelial cells metabolize glutamine to glutamate, generating ammonium that is excreted in the urine and bicarbonate that is absorbed into the blood. This process is responsible for the vast majority of renal acid excretion in chronic acidotic states.

References

- Renal ammonia metabolism and transport.

Biochemistry	Renal, Urinary Systems & Electrolytes	Metabolic acidosis
Subject	System	Topic

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Biochemistry	Renal, Urinary Systems & Electrolytes	Metabolic acidosis
Subject	System	Topic

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A 38-year-old man comes to the office due to pain in multiple joints. He has a 5-year history of lumbar pain and a 2-year history of bilateral knee pain. The patient works in construction and his pain is worst after a long day on his feet. He has taken ibuprofen intermittently, but the pain is no longer tolerable. The patient has a paternal aunt with osteoarthritis. Physical examination shows blue-black spots on his sclerae and diffuse darkening of the auricular helices. Which of the following is the most likely cause of this patient's arthritis?

- A. Homogentisic acid dioxygenase deficiency
- B. Hyperuricemia
- C. Multifactorial articular cartilage failure
- D. Recent infection with *Salmonella*
- E. Tyrosinase deficiency

Submit

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- ✓ A. Homogentisic acid dioxygenase deficiency (69%)
- B. Hyperuricemia (3%)
- C. Multifactorial articular cartilage failure (18%)
- D. Recent infection with *Salmonella* (0%)
- E. Tyrosinase deficiency (6%)

Omitted
Correct answer
A

69%
Answered correctly

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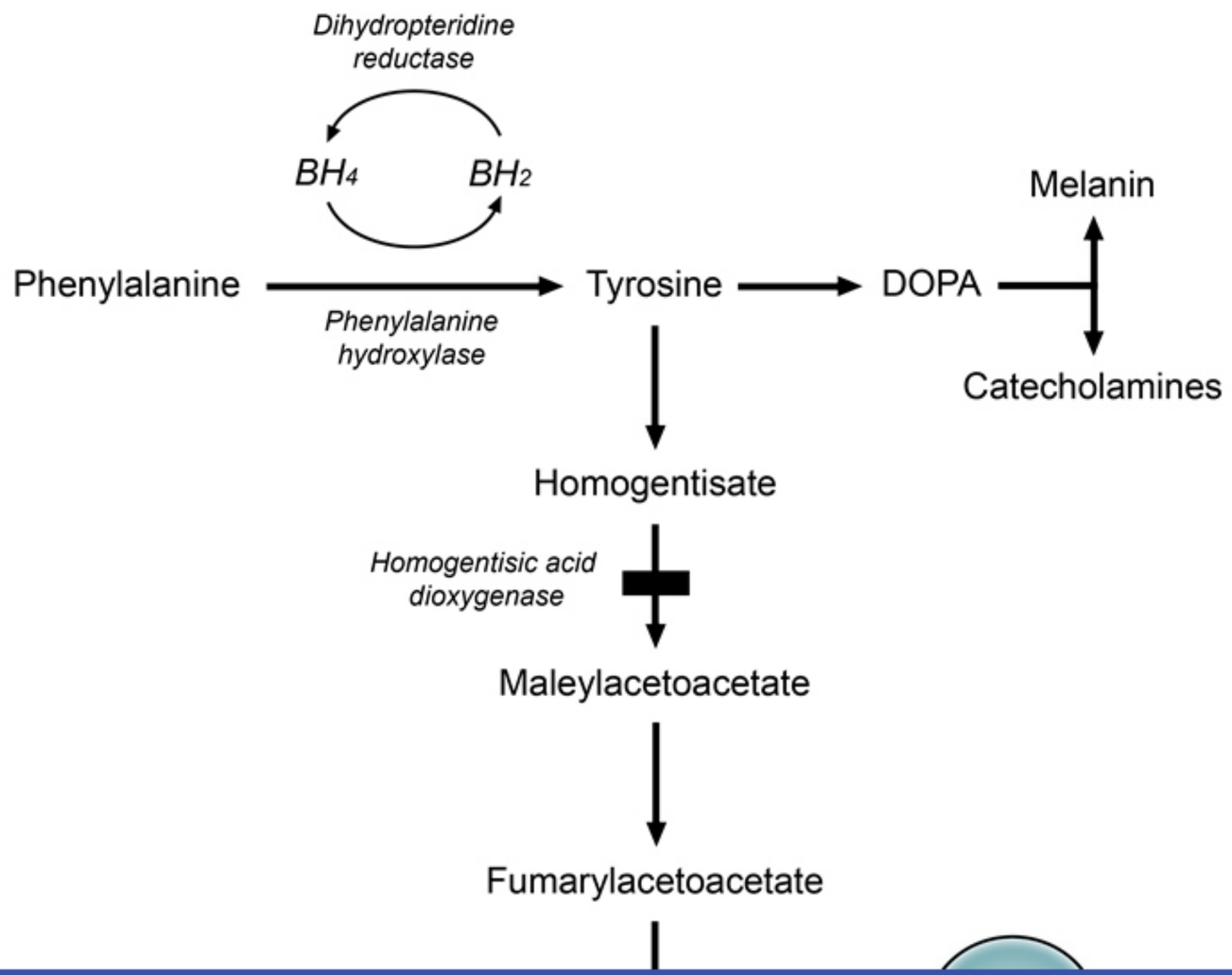
Last Updated

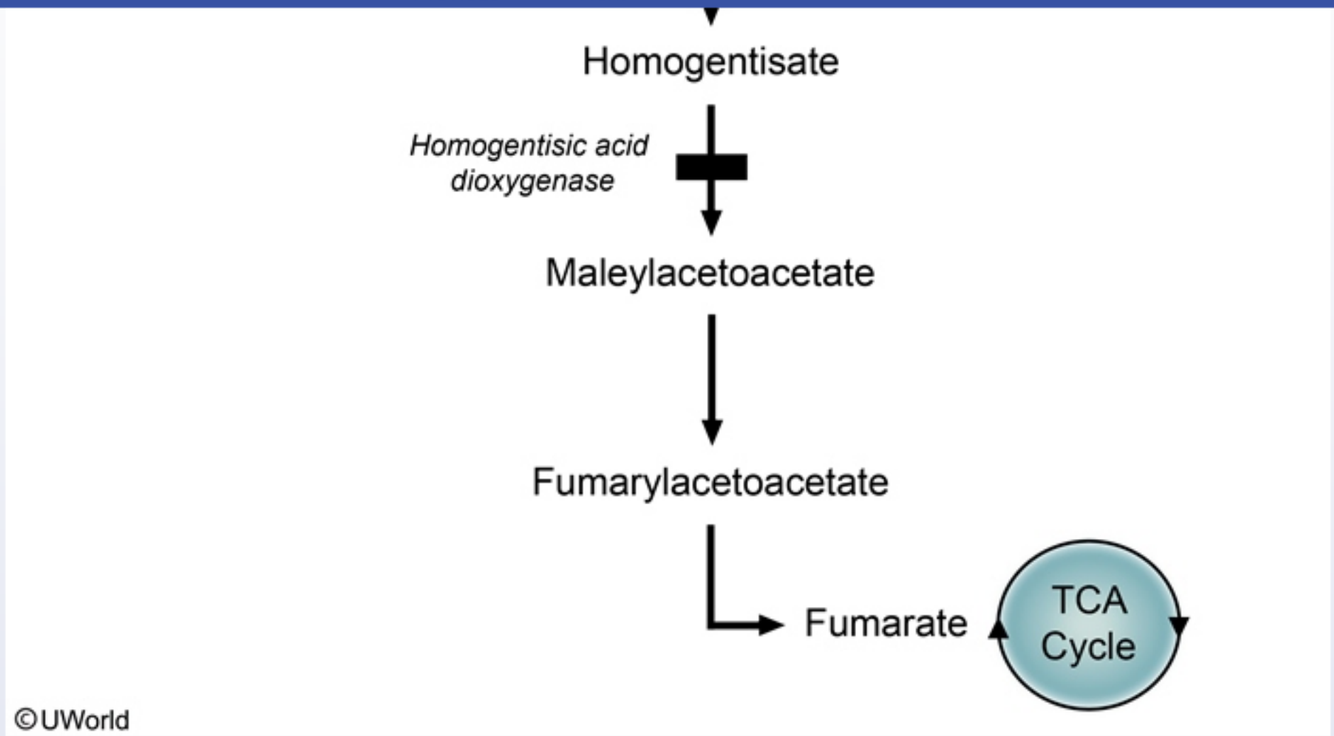
Explanation

Alkaptonuria

Dihydropteridine reductase

Alkaptonuria





Alkaptonuria is a relatively benign childhood disorder that is marked by severe **arthritis** in adult life. This **autosomal-recessive** disorder is caused by **deficiency of homogentisic acid dioxygenase**, which normally metabolizes homogentisic acid into maleylacetoacetate. Accumulated homogentisic acid causes pigment deposits in **connective tissue** throughout the body. During adulthood, these **blue-black deposits** become apparent in the sclerae and ear cartilage. Deposits also occur in the large joints and spine, causing ankylosis, motion restriction, and significant pain. A distinctive characteristic of alkaptonuria is that the urine of these patients turns black when exposed to air due to oxidization of homogentisic acid.

(Choice B) Hyperuricemia can cause acute monoarticular gouty arthritis due to urate crystal deposition in joints (usually the great toe or knee). These acute attacks resolve in days to weeks and are not associated with connective tissue hyperpigmentation.

(Choice C) Osteoarthritis is due to combined genetic, metabolic, and mechanical factors that result in defects in articular cartilage. Polyarticular

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(Choice C) Osteoarthritis is due to combined genetic, metabolic, and mechanical factors that result in defects in articular cartilage. Polyarticular joint involvement of the fingers (including Heberden and Bouchard nodes), knees, hips, and spine classically occur. Joint pain typically peaks in the afternoon or evening after activity, but osteoarthritis is not associated with the blue-black deposits.

(Choice D) Reactive arthritis can occur following enteric or genitourinary infections with organisms such as *Salmonella*, *Shigella*, *Campylobacter*, and *Chlamydia*. The typical pattern is asymmetric involvement of lower extremity joints accompanied by enthesitis (inflammation at insertion of tendons), conjunctivitis, and urethritis. Reactive arthritis has no associated skin findings in contrast to alkaptonuria.

(Choice E) Albinism is caused by defects in biosynthesis and distribution of melanin. Melanocytes synthesize melanin from tyrosine via the enzyme tyrosinase.

Educational objective:
Alkaptonuria is an autosomal-recessive disorder caused by a deficiency of homogentisic acid dioxygenase, an enzyme involved in tyrosine metabolism. Excess homogentisic acid causes diffuse blue-black deposits in connective tissues. Adults have sclerae and ear cartilage hyperpigmentation along with osteoarthropathy of the spine and large joints.

References

- Alkaptonuria.
- Alkaptonuria.

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References

- Alkaptonuria.
- Alkaptonuria.

Biochemistry	Rheumatology/Orthopedics & Sports	Alkaptonuria
Subject	System	Topic

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A 6-month-old boy is brought to the office by his mother out of concern that he is not developing normally. He has been feeding regularly and has had no medical problems other than a mild respiratory infection a month earlier. However, the mother says, "he doesn't seem to be as interactive as my other children were at his age." Physical examination reveals delayed developmental milestones and hypotonia. Two years later, the child is found to have involuntary movements and demonstrates a tendency to aggressively bite his own lips and fingers. Laboratory analysis shows an elevated blood uric acid level. Activity of which of the following enzymes is most likely increased as a result of this patient's condition?

- A. Aspartate carbamoyltransferase
- B. Dihydroorotase
- C. Hypoxanthine-guanine phosphoribosyltransferase
- D. Phosphoribosyl pyrophosphate amidotransferase
- E. Ribonucleotide reductase
- F. Thymidylate synthase

Submit

A 6-month-old boy is brought to the office by his mother out of concern that he is not developing normally. He has been feeding regularly and has had no medical problems other than a mild respiratory infection a month earlier. However, the mother says, "he doesn't seem to be as interactive as my other children were at his age." Physical examination reveals delayed developmental milestones and hypotonia. Two years later, the child is found to have involuntary movements and demonstrates a tendency to aggressively bite his own lips and fingers. Laboratory analysis shows an elevated blood uric acid level. Activity of which of the following enzymes is most likely increased as a result of this patient's condition?

- A. Aspartate carbamoyltransferase (4%)
- B. Dihydroorotase (3%)
- C. Hypoxanthine-guanine phosphoribosyltransferase (43%)
- ✓ D. Phosphoribosyl pyrophosphate amidotransferase (40%)
- E. Ribonucleotide reductase (3%)
- F. Thymidylate synthase (3%)

Omitted
Correct answer
D

40%
Answered correctly

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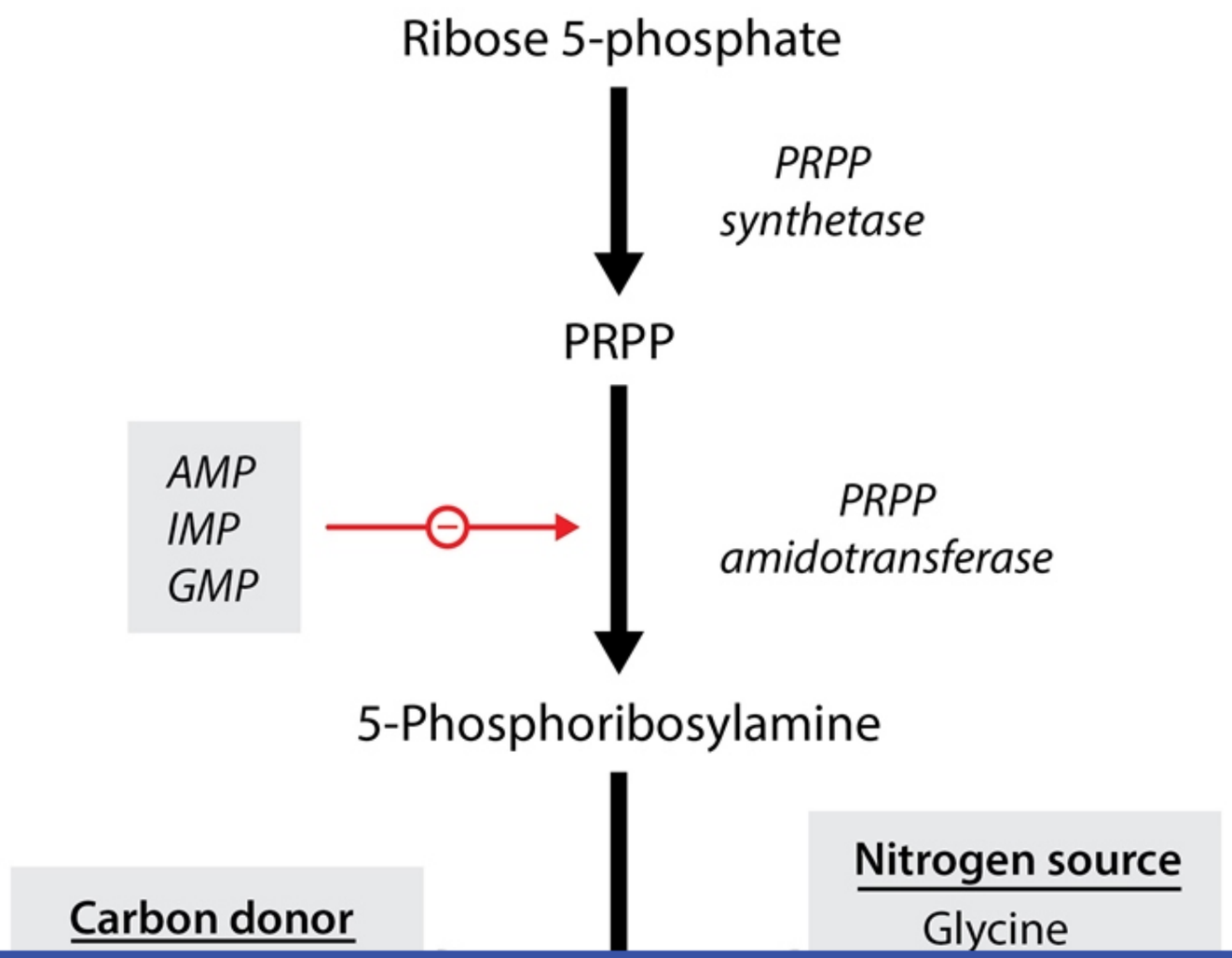
Last Updated

Explanation

De novo purine synthesis

De novo purine synthesis



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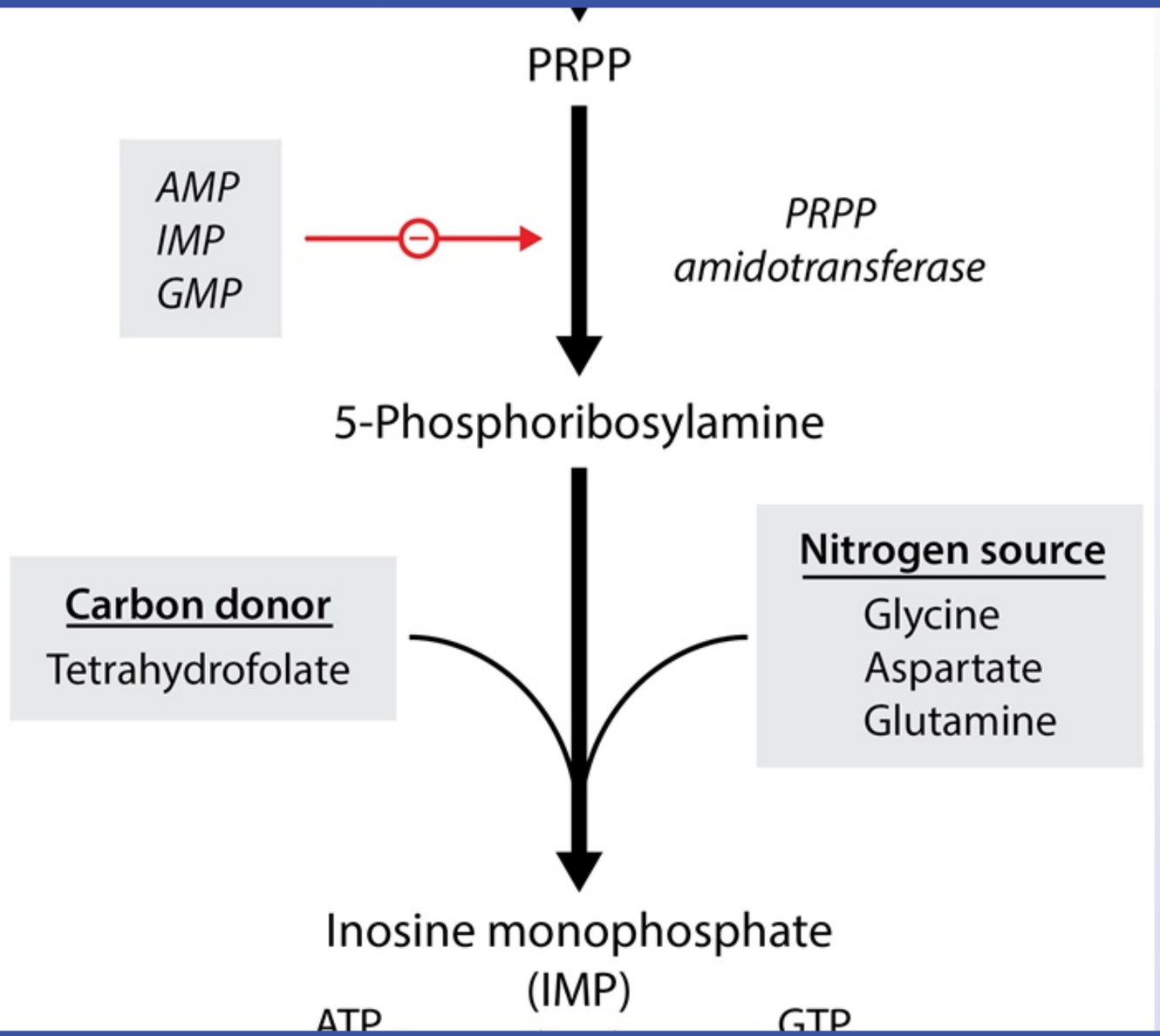

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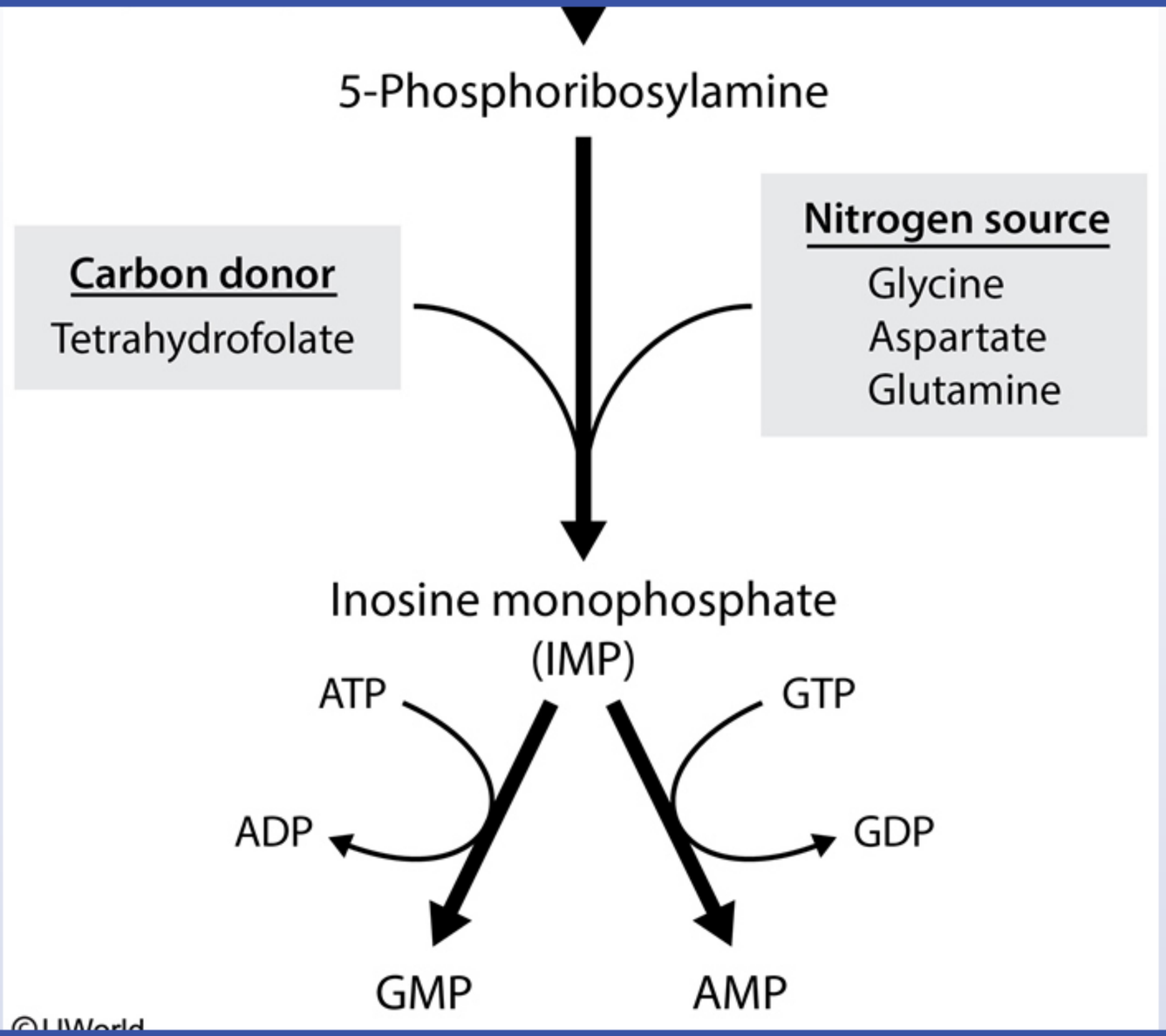

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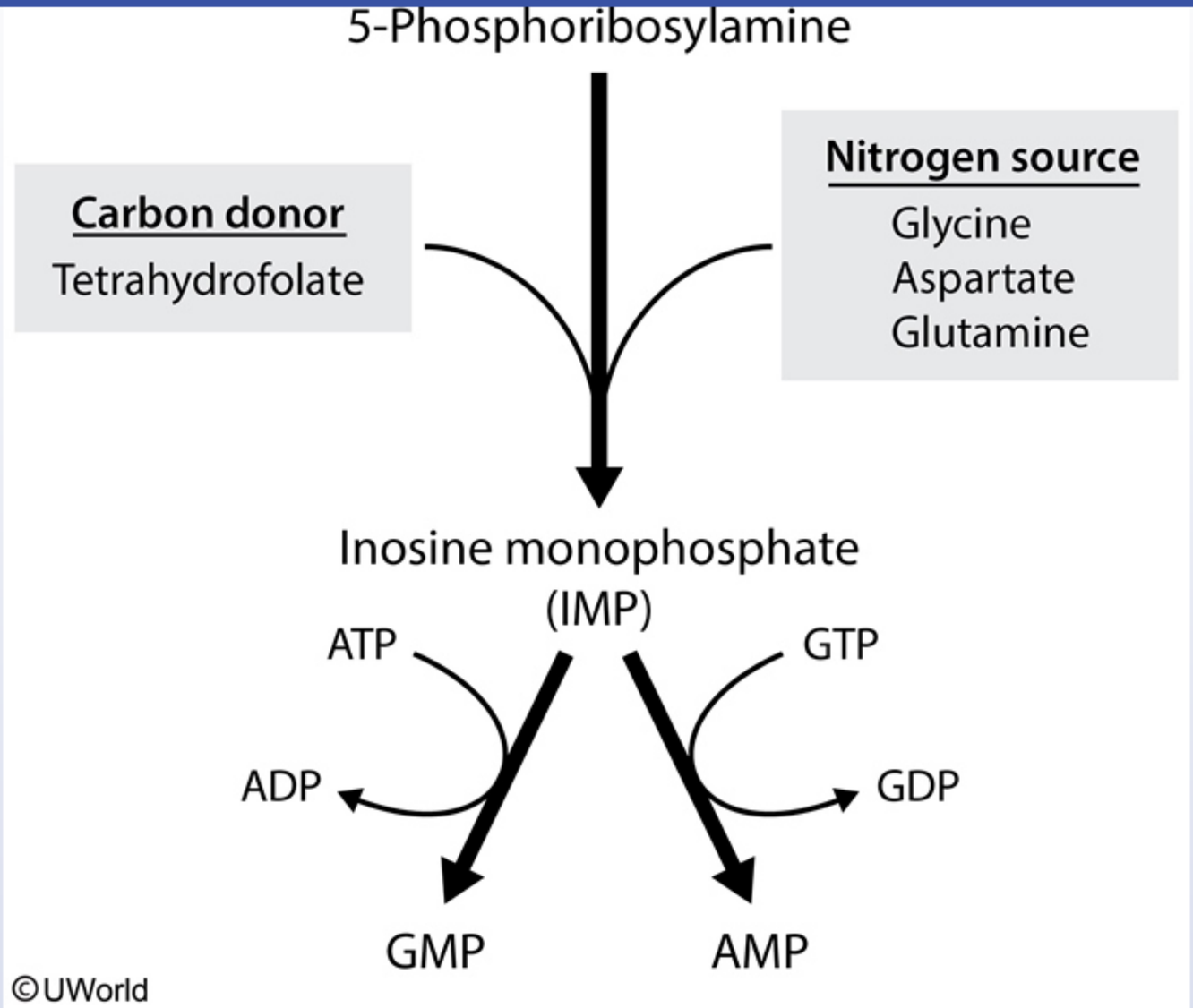

This patient has **Lesch-Nyhan syndrome**, an X-linked recessive disorder characterized by the development of dystonia, choreoathetosis, **self-**

This patient has **Lesch-Nyhan syndrome**, an X-linked recessive disorder characterized by the development of dystonia, choreoathetosis, **self-mutilation**, and **hyperuricemia** within the first few years of life. The condition is caused by deficiency of **hypoxanthine-guanine phosphoribosyltransferase** (HGPRT), an enzyme that normally functions in the purine salvage pathway to convert hypoxanthine back to inosine monophosphate and guanine back into guanosine monophosphate. The absence of HGPRT results in increased degradation of guanine and hypoxanthine bases into uric acid, which **increases** the demand for **de novo purine synthesis**.

The first step of purine synthesis is the formation of phosphoribosyl pyrophosphate (PRPP) by PRPP synthetase. PRPP can be used by adenine phosphoribosyltransferase and HGPRT for purine salvage, or it can be converted to phosphoribosylamine by PRPP amidotransferase in the first committed step of de novo purine synthesis. Because purine salvage is impaired in Lesch-Nyhan syndrome, the **activity of PRPP amidotransferase must increase** to supply a sufficient quantity of purine nucleotides.

(Choices A, B, and F) These enzymes are involved in pyrimidine synthesis. Their activity would not be significantly altered in Lesch-Nyhan syndrome, which impairs purine salvage.

(Choice C) The activity of HGPRT is decreased (not increased) in Lesch-Nyhan syndrome.

(Choice E) Purine and pyrimidine nucleotides are initially synthesized as bases attached to a ribose sugar. The enzyme ribonucleotide reductase converts ribose sugars to their deoxyribose forms for use in DNA synthesis. This enzyme is negatively regulated by accumulation of deoxyribose nucleotides; its activity is determined primarily by the cellular proliferation rate (increased cell division requires more deoxyribose nucleotides).

Educational objective:
Lesch-Nyhan syndrome is an X-linked recessive disorder caused by a defect in hypoxanthine-guanine phosphoribosyltransferase (HGPRT). This results in failure of the purine salvage pathway, leading to increased degradation of hypoxanthine and guanine to uric acid. De novo purine synthesis must increase to replace the lost bases, necessitating an increase in phosphoribosyl pyrophosphate (PRPP) amidotransferase activity.

Biochemistry	Nervous System	Lesch Nyhan Syndrome
Subject	System	Topic

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A 35-year-old female is hospitalized with headaches and vomiting. She has a long history of psychiatric illness and is known to practice eccentric dietary habits. Physical findings include papilledema, dry skin and hepatosplenomegaly. Head CT scan is ordered immediately but is negative for intracranial mass. Which of the following is a likely cause of this patient's condition?

- A. Thiamine deficiency
- B. Niacin deficiency
- C. Vitamin B_{12} deficiency
- D. Riboflavin deficiency
- E. Vitamin C overuse
- F. Vitamin E overuse
- G. Vitamin A overuse

Submit

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- A. Thiamine deficiency (8%)
- B. Niacin deficiency (11%)
- C. Vitamin B_{12} deficiency (5%)
- D. Riboflavin deficiency (4%)
- E. Vitamin C overuse (2%)
- F. Vitamin E overuse (5%)
- ✓ G. Vitamin A overuse (61%)

Omitted
Correct answer
G

61%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

Individuals who consume more than 10 times the Daily Value (Recommended Dietary Allowance) of vitamin A are prone to developing toxicity and may suffer hepatic injury so severe as to cause cirrhosis.

Vitamin A toxicity has been subdivided into three syndromes: acute, chronic, and teratogenic. The signs and symptoms of acute toxicity occur

Individuals who consume more than 10 times the Daily Value (Recommended Dietary Allowance) of vitamin A are prone to developing toxicity and may suffer hepatic injury so severe as to cause cirrhosis.

Vitamin A toxicity has been subdivided into three syndromes: acute, chronic, and teratogenic. The signs and symptoms of acute toxicity occur after the ingestion of a single high dose of vitamin A and include nausea, vomiting, vertigo, and blurred vision. The signs and symptoms of chronic toxicity occur after the long-term ingestion of high doses of vitamin A, and include alopecia, dry skin, hyperlipidemia, hepatotoxicity, hepatosplenomegaly, and visual difficulties. Papilledema, when present, is suggestive of cerebral edema in the setting of benign intracranial hypertension (pseudotumor cerebri). Teratogenic effects of excessive vitamin A ingestion include microcephaly, cardiac anomalies, and fetal death (especially in the first trimester of pregnancy).

(Choice A) Thiamine deficiency is associated with infantile and adult beriberi, as well as Wernicke-Korsakoff syndrome in alcoholics.

(Choice B) Niacin deficiency is characterized by the 3 D's of pellagra: (dementia, dermatitis, and diarrhea).

(Choice C) Vitamin B_{12} (cobalamin) deficiency is frequently associated with pernicious anemia. The classic presentation of pernicious anemia is an older, mentally slow woman of northern European descent who is "lemon colored" (anemic and icteric), has a smooth, shiny tongue indicative of atrophic glossitis, and demonstrates a shuffling broad-based gait.

(Choice D) Vitamin B2 (riboflavin) deficiency is characterized by cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization, and ariboflavinosis.

(Choice E) Large doses of vitamin C can give false negative stool guaiac results and are associated with diarrhea and abdominal bloating. Some studies suggest an association between high doses of vitamin C and calcium oxalate nephrolithiasis, though this remains controversial.

(Choice F) Large doses of vitamin E have been associated with higher mortality rates due to hemorrhagic stroke in adults and higher rates of necrotizing enterocolitis in infants.

Educational Objective:
Vitamin A overuse can result in intracranial hypertension, skin changes and hepatosplenomegaly.

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Educational Objective:
Vitamin A overuse can result in intracranial hypertension, skin changes and hepatosplenomegaly.

Biochemistry	Nervous System	Vitamin a toxicity
Subject	System	Topic

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Molecular biologists studying the properties of hemoglobin are investigating the structural changes associated with oxygen loading and unloading. During the transition from point 1 to point 2 on the graph shown below, hemoglobin molecules are most likely to release which of the following?

A. Chloride

B. Heme

C. Oxygen

D. Phosphate

E. Protons

Submit

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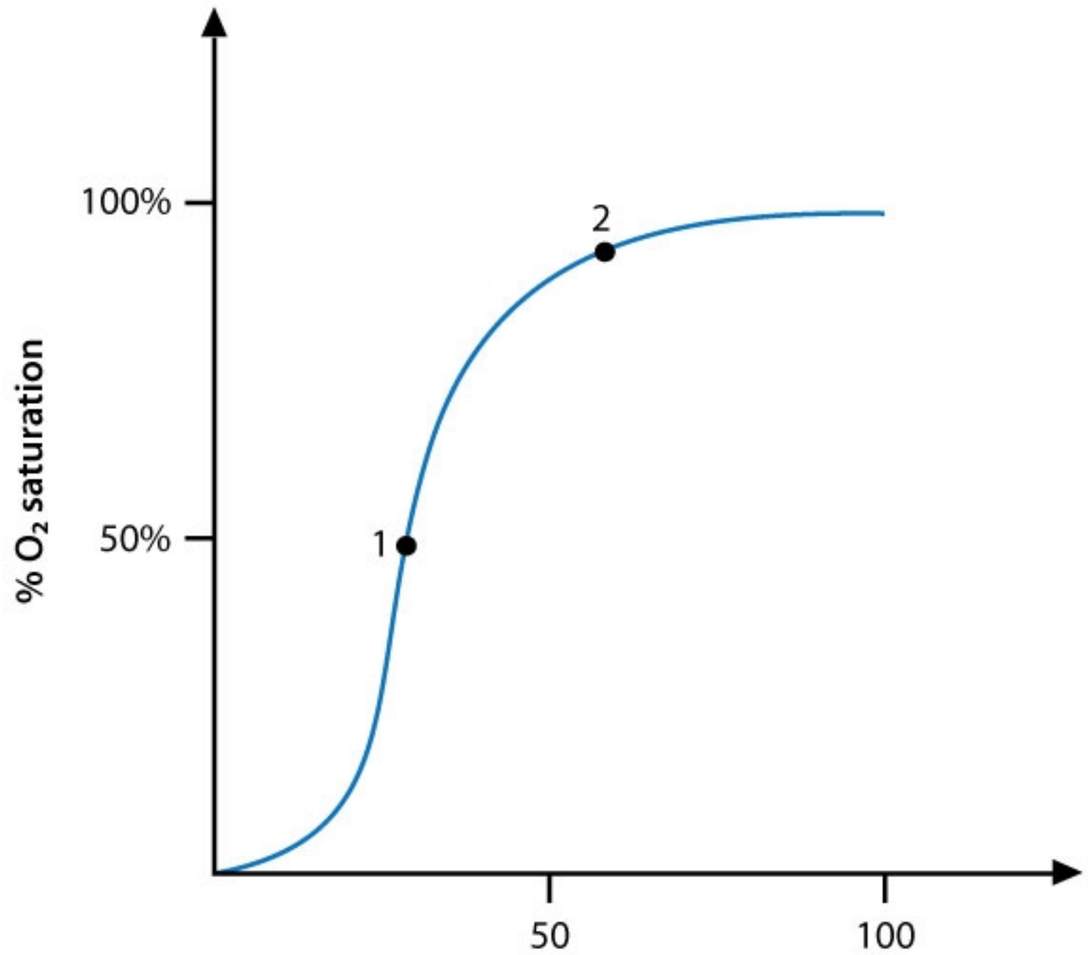

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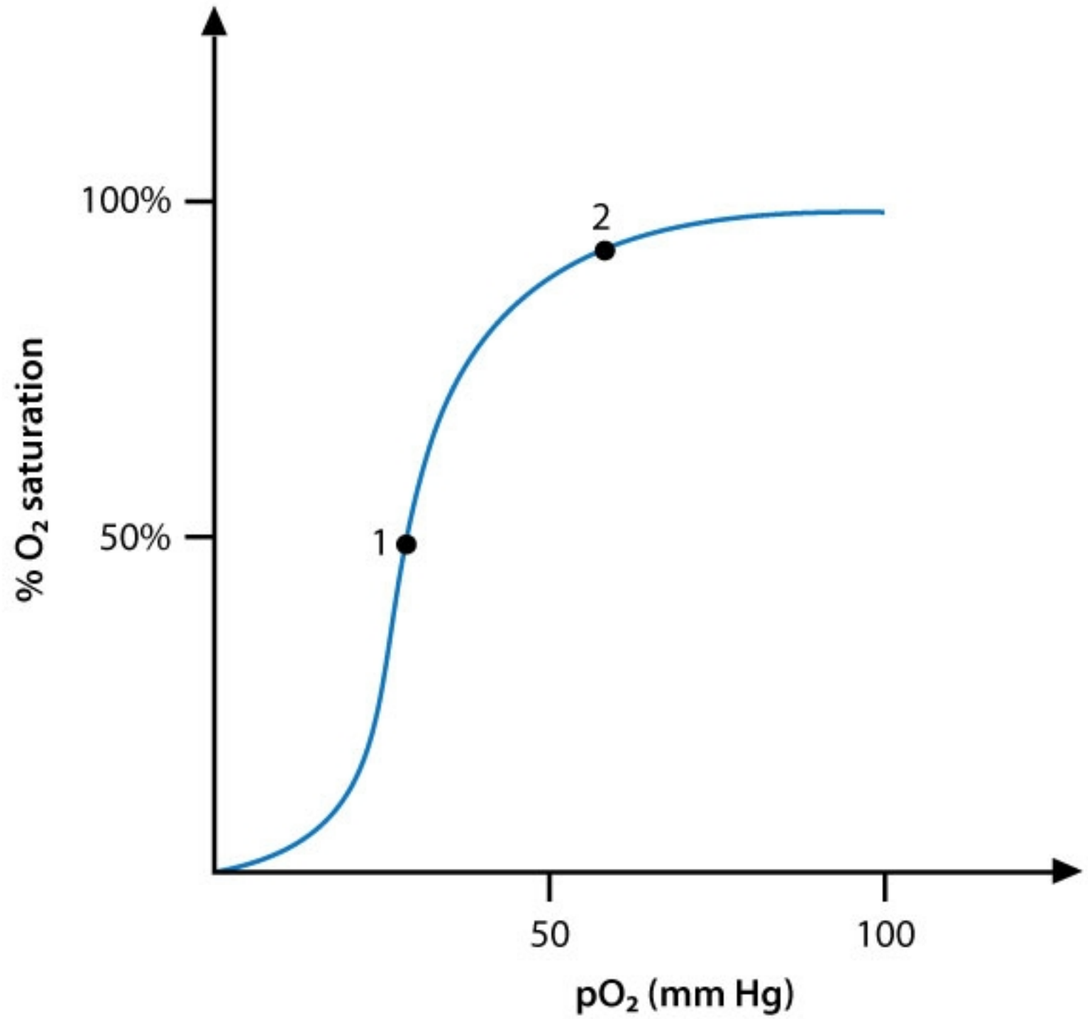

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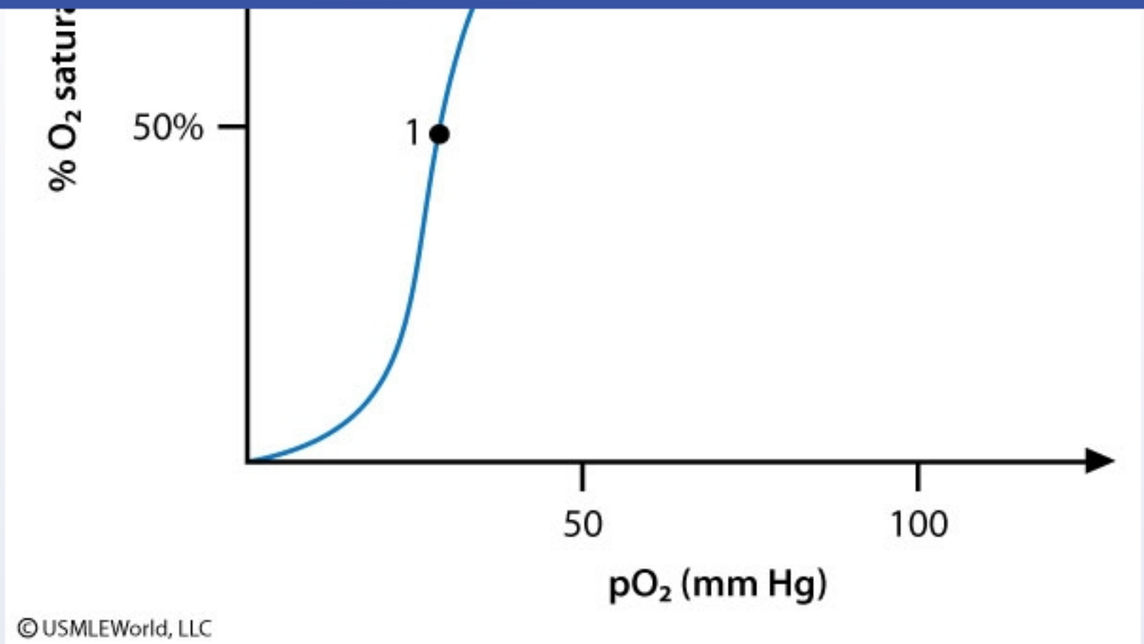
A Chloride



A. Chloride
B. Heme
C. Oxygen
D. Phosphate
E. Protons

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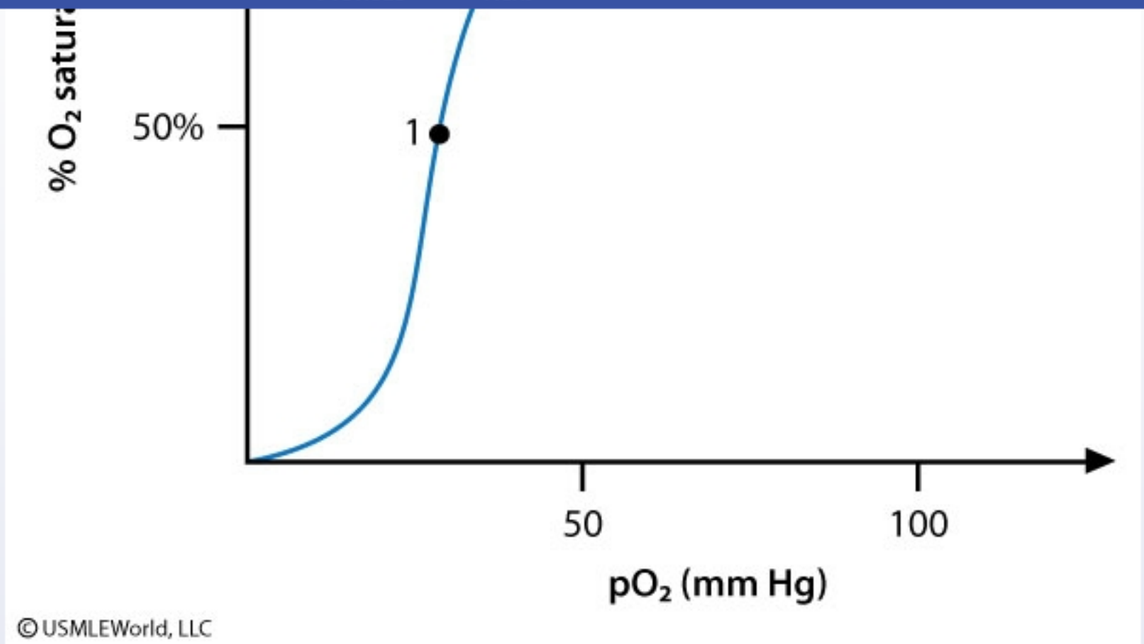

A. Chloride (13%)

B. Heme (1%)

C. Oxygen (19%)

D. Phosphate (6%)

✓ E. Protons (57%)

Omitted
Correct answer

57%
Answered correctly

08 secs
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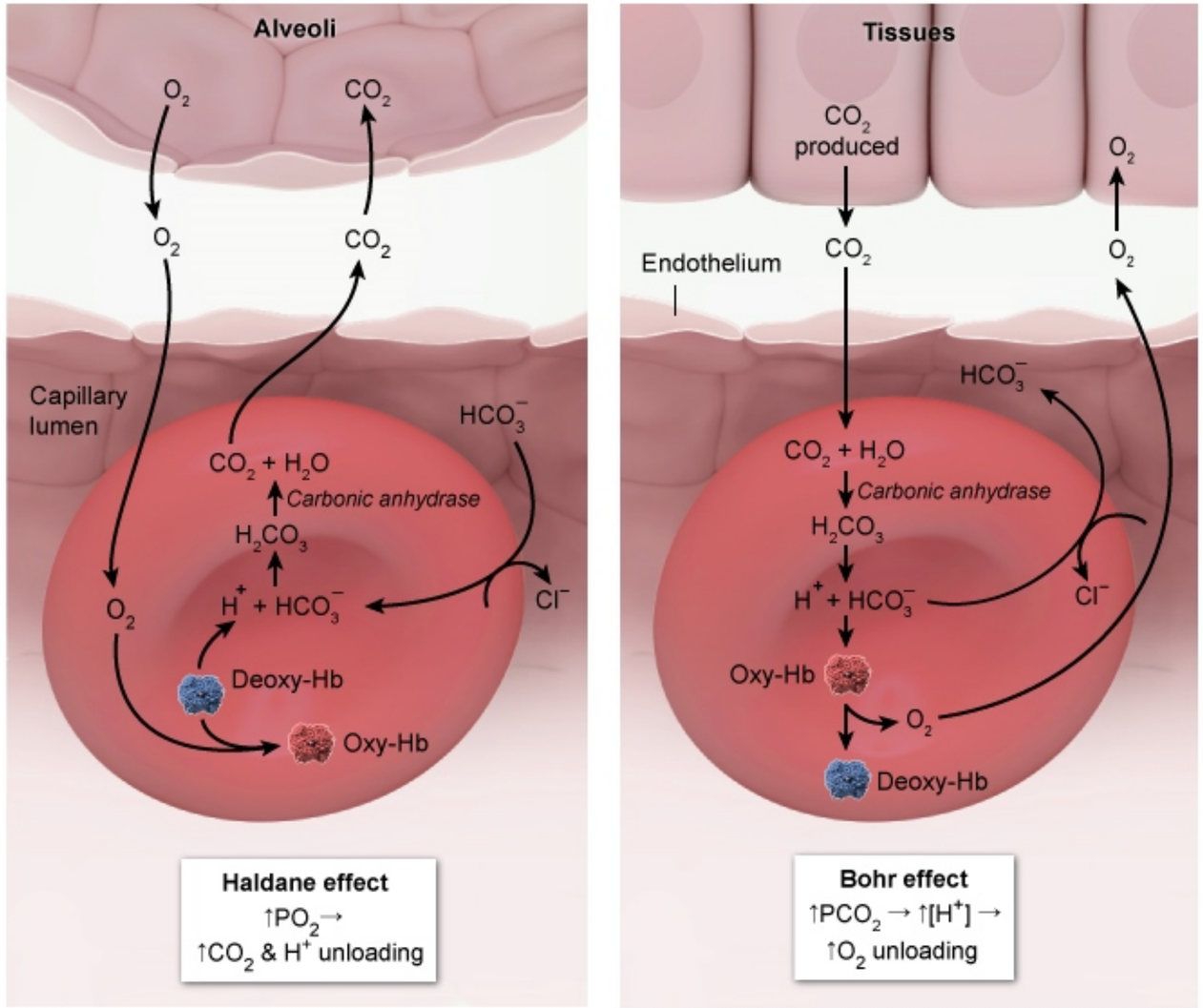
The Haldane & Bohr effects



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The transition from point 1 to 2 on the graph represents the loading of O_2 onto partially deoxygenated hemoglobin as occurs in the **lungs**. At very low partial pressure of O_2 (pO_2), hemoglobin is mostly deoxygenated, and binding of O_2 molecules is relatively difficult (as indicated by the early flatness of the curve). As the partial pressure of O_2 increases, O_2 binds to 1 of the 4 binding sites on hemoglobin and **increases the O_2-binding affinity** of the other available binding sites (steepening of the curve), a phenomenon known as **cooperative binding**. Subsequently, additional O_2 molecules bind more easily as the pO_2 increases until hemoglobin becomes nearly fully saturated.

The binding of O_2 molecules to hemoglobin in the lungs has two consequences, known as the **Haldane effect**:

- The affinity of hemoglobin for CO_2 is decreased, resulting in unloading of CO_2 from hemoglobin (this accounts for a small percentage of overall CO_2 in the blood and is not pictured above).
- The acidity of the hemoglobin molecule is increased; in response, **protons (H^+ ions) are released** from the hemoglobin binding sites.

The H^+ ions combine with bicarbonate ions (the primary form of CO_2 in the blood) in the lungs to facilitate the production of water (H_2O) and CO_2. The CO_2 is then transferred to the alveoli and expired while oxygen is taken up by hemoglobin.

In the peripheral tissues, high levels of CO_2 create an increase in ambient acidity that shifts the hemoglobin dissociation curve to the right and facilitates the unloading of O_2 (**Bohr effect**). The CO_2 (and water) are converted into H^+ and HCO_3^-. The H^+ ions are carried by hemoglobin while the HCO_3^- is transferred to the plasma for transport back to the lungs.

(Choice A) In the lungs, chloride ions shift out of red blood cells and into the plasma in exchange for HCO_3^-. These chloride ions are not bound to or released by hemoglobin.

(Choice B) Heme is not released from hemoglobin during O_2 loading or unloading. However, it is released during the normal destruction of aged red blood cells in the spleen.

(Choice C) O_2 molecules bind to hemoglobin to increase hemoglobin saturation.

(Choice D) 2,3-diphosphoglycerate contains 2 phosphate groups and binds to hemoglobin to facilitate unloading of O_2 in the tissues. However, phosphate molecules are not directly bound or released by hemoglobin.

Educational objective:

The binding of O_2 to hemoglobin increases the affinity for binding of subsequent O_2 molecules (cooperative binding). In the lungs, the binding of

overall CO_2 in the blood and is not pictured above).

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Educational objective:
The binding of O_2 to hemoglobin increases the affinity for binding of subsequent O_2 molecules (cooperative binding). In the lungs, the binding of O_2 to hemoglobin drives the release of H^+ and CO_2 from hemoglobin (Haldane effect). In the peripheral tissues, high concentrations of CO_2 and H^+ facilitate O_2 unloading from hemoglobin (Bohr effect).

Biochemistry	Pulmonary & Critical Care	Respiratory physiology
Subject	System	Topic

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Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein- dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

A. Ca^{2+}

B. cAMP

C. cGMP

D. Cl^-

E. mRNA

F. NO

Submit

Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein- dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

- ✓ A. Ca^{2+} (77%)
- B. cAMP (10%)
- C. cGMP (9%)
- D. Cl^- (0%)
- E. mRNA (0%)
- F. NO (1%)

Omitted
Correct answer
A

77%
Answered correctly

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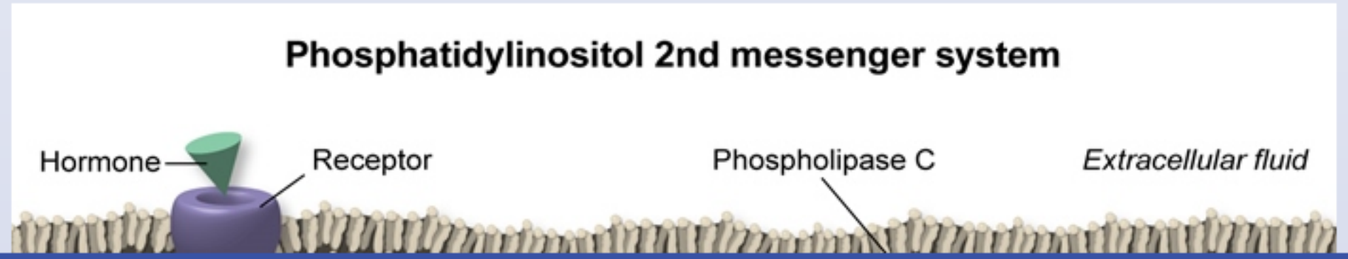
Time Spent

01/19/2020
Last Updated

Explanation



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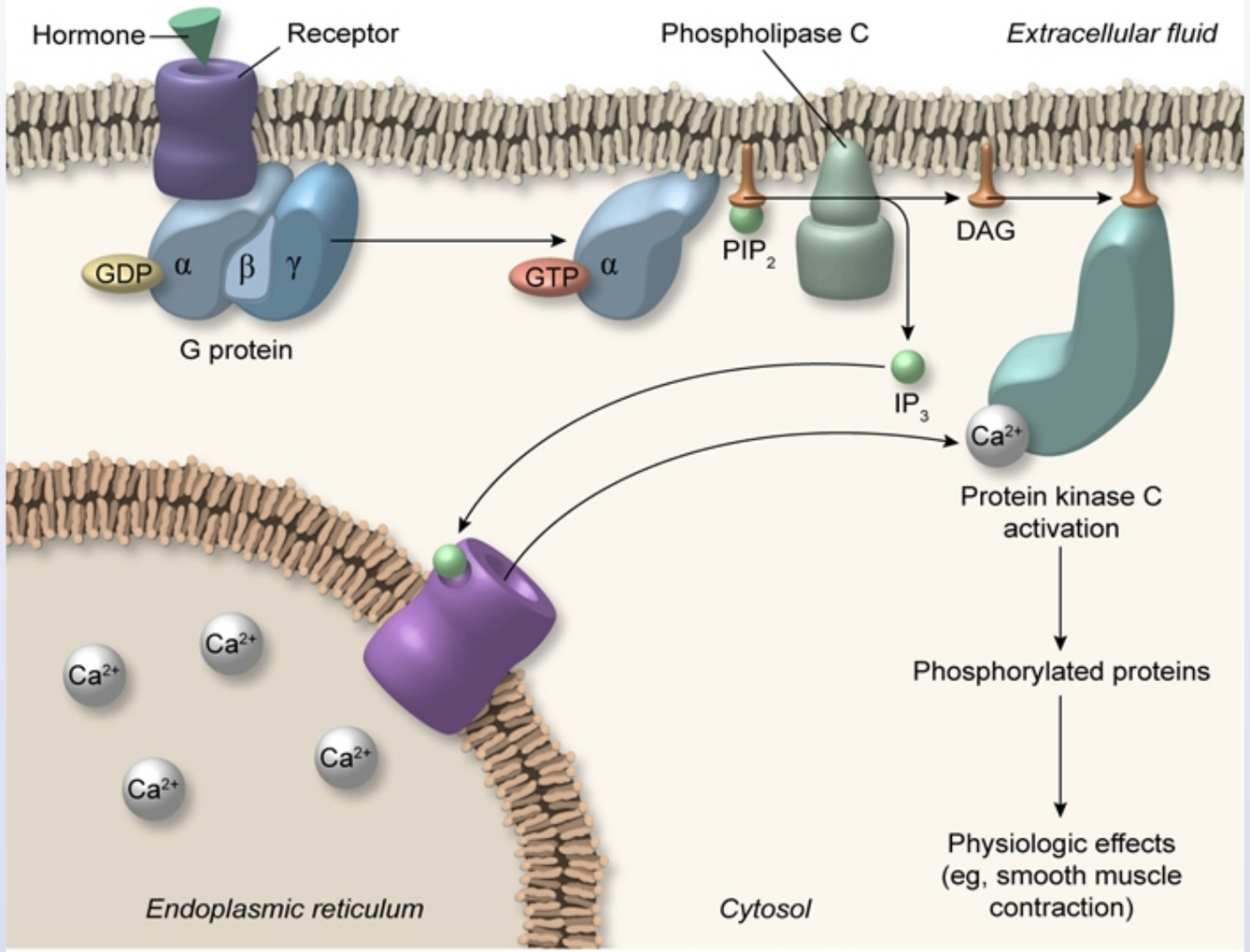
Phosphatidylinositol 2nd messenger system



DAG = diacylglycerol; GDP = guanosine 5' diphosphate; GTP = guanosine 5' triphosphate;

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A variety of hormone receptors are known to exert their intracellular effects via the **phosphoinositol system**. Examples include α_1-adrenergic, M_1 and M_3 cholinergic, V_1 (vasopressin), H_1 (histamine), oxytocin, angiotensin II, TRH, and GnRH receptors. This signal transduction pathway proceeds through the following steps:

1. Binding of a ligand to its cell surface receptor causes the **exchange of GDP for GTP** on the α-subunit of a **G_q-protein** associated with the receptor. The activated α-subunit undergoes a conformational change and exposes a **phospholipase C** (PLC) activating site.
2. After activation, PLC hydrolyzes **phosphatidyl inositol bisphosphate** (PIP_2) into **diacylglycerol** (DAG) and **inositol triphosphate** (IP_3).
3. DAG is able to directly stimulate **protein kinase C** (PKC), but the major activator of PKC is **increased intracellular Ca^{2+}** that occurs due to IP_3 mediated-release of intracellular Ca^{2+} stores from the endoplasmic reticulum. PKC is the major effector molecule in this pathway; it directly modulates the activity of other proteins via phosphorylation.

(Choices B and C) Intracellular cAMP and cGMP concentrations increase during activation of adenylate or guanylate cyclase second messenger systems, respectively. Levels can also increase following cyclic nucleotide phosphodiesterase inhibition, as seen on exposure to sildenafil, which selectively inhibits cGMP phosphodiesterase and results in smooth muscle relaxation in blood vessels.

(Choice D) Intracellular Cl^- concentration increases slightly after inhibitory neurotransmitters (eg, GABA, glycine) act on the neuron to increase Cl^- membrane conductance (hyperpolarization).

(Choice E) The intracellular concentration of mRNA increases during cellular states of elevated protein synthesis (eg, during cell division).

(Choice F) Nitric oxide (NO) is a paracrine signaling molecule with a lifetime of a few seconds. It can freely cross cell membranes and functions as a critical component of endothelium-mediated vasodilation. NO is synthesized from arginine and O_2 by the enzyme NO-synthase.

Educational objective:
The phosphoinositol second messenger system begins with ligand-receptor binding and G_q-protein activation leading to activation of phospholipase C (PLC). PLC then hydrolyzes phosphatidyl inositol bisphosphate and forms diacylglycerol and inositol triphosphate (IP_3). Finally, IP_3 activates protein kinase C via an increase in intracellular Ca^{2+}.

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Biochemistry	Miscellaneous (Multisystem)	Signal transduction
Subject	System	Topic

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A 55-year-old farmer is brought to the emergency department after his daughter found him confused and disoriented in the tool shed at home. He has been otherwise healthy and does not take any medications. On physical examination, blood pressure is 110/70 mm Hg and pulse is 50/min. The patient's pupils are symmetric, 2 mm, and reactive to light. His eyes are tearing considerably. There are scattered wheezes bilaterally on lung auscultation. The patient's skin is clammy and he is sweating profusely. Impairment of which of the following steps at the neuromuscular junction is most likely responsible for his presentation?

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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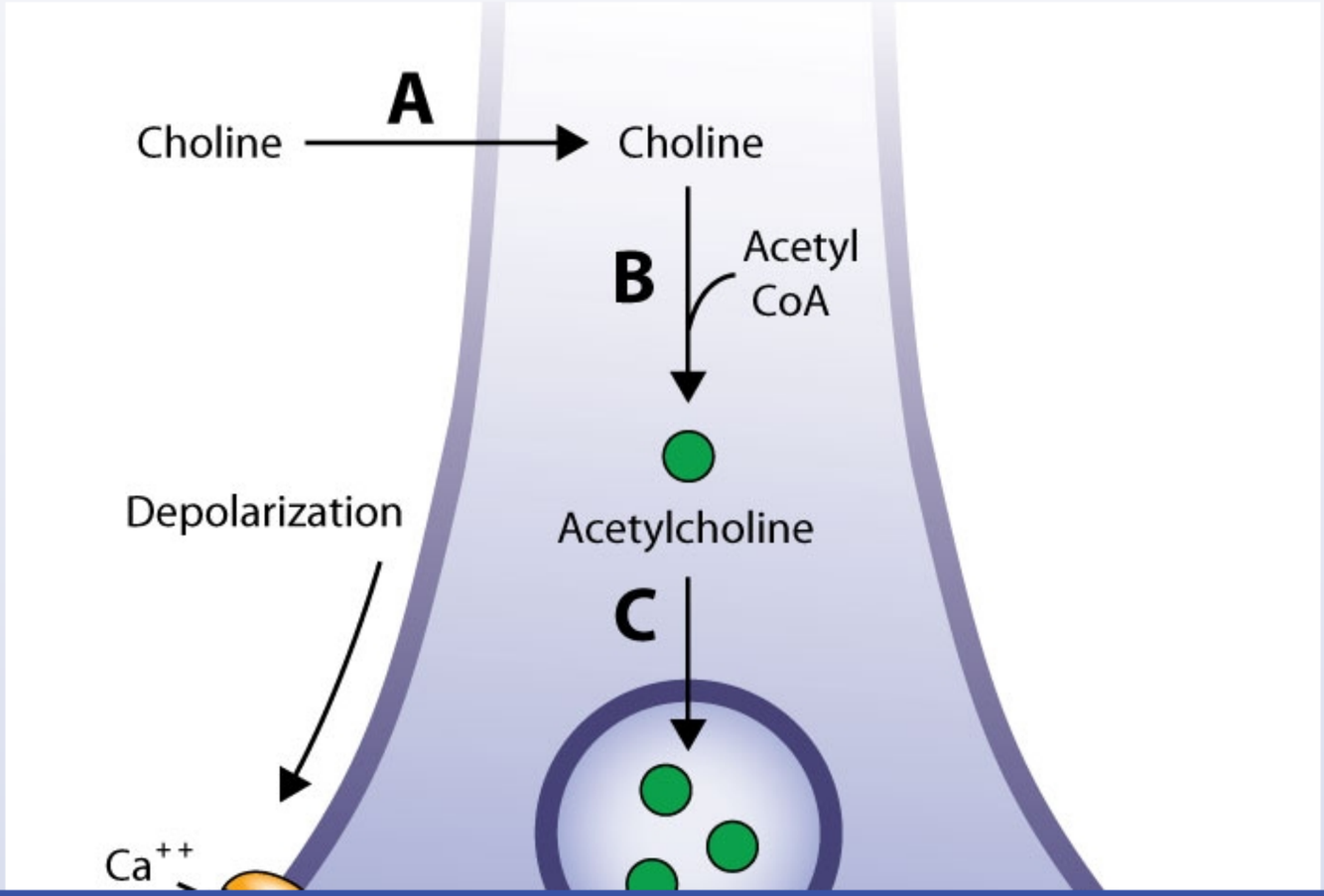

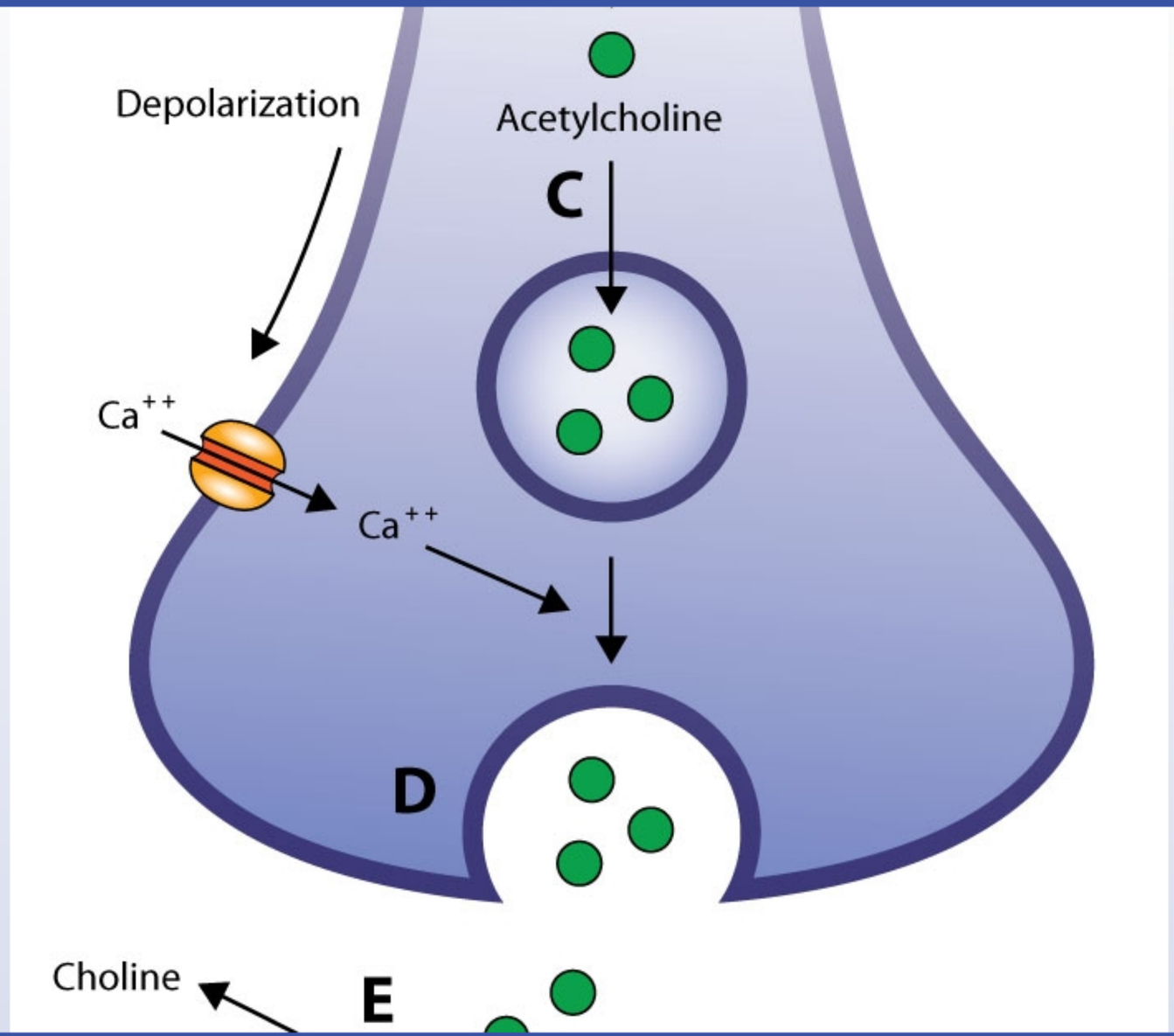
Depolarization
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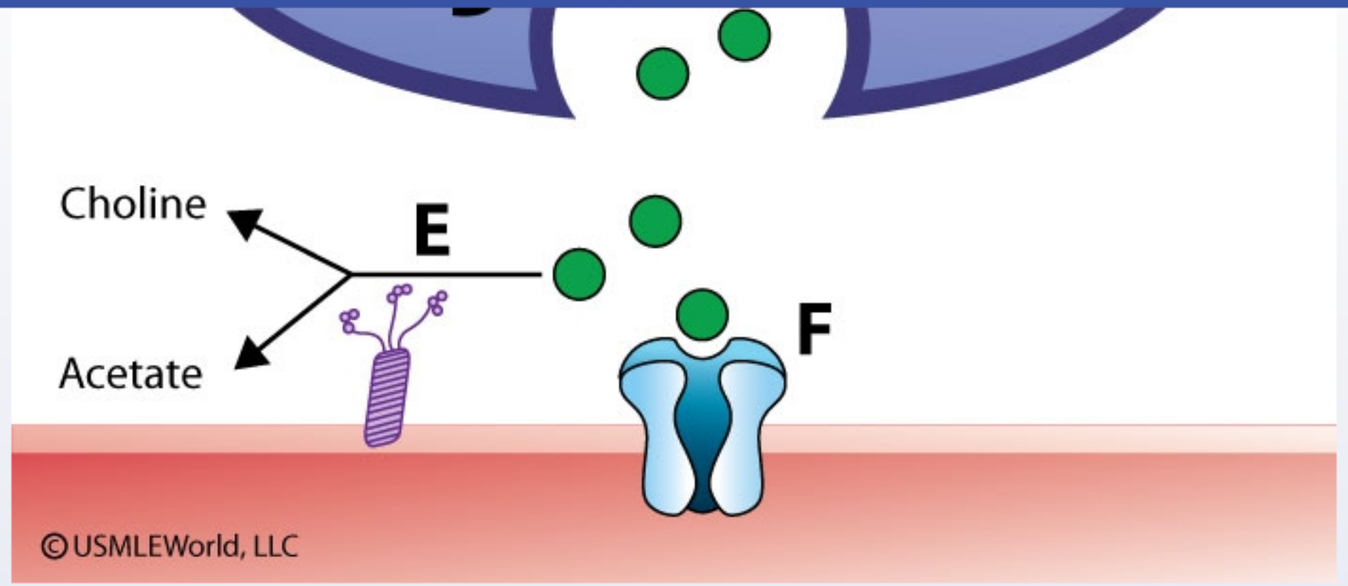

A. A
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C. C
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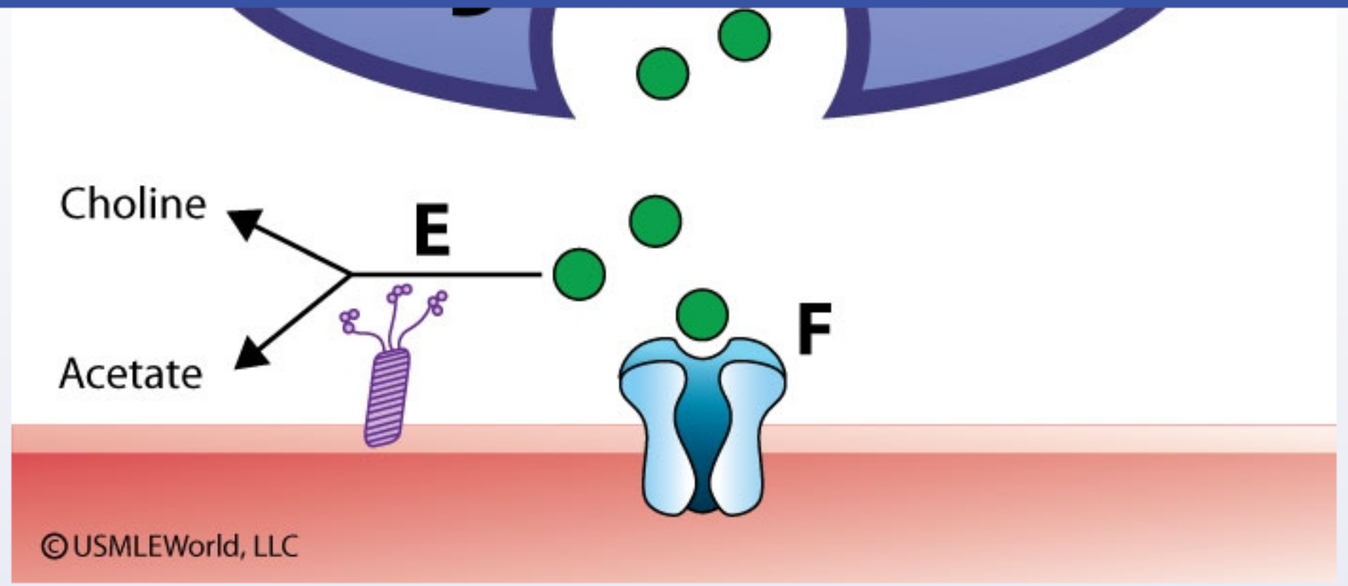

A. A (0%)
B. B (1%)
C. C (1%)
D. D (5%)
✓ E. E (84%)
F. F (6%)

Omitted
Correct answer

84%
Answered correctly

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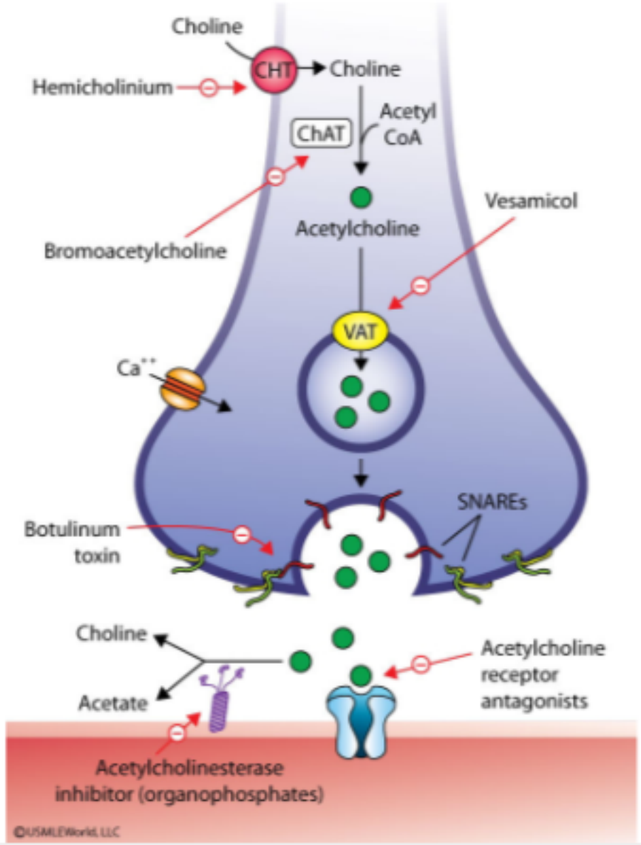
Exhibit Display

Inhibitors of acetylcholine neurotransmission



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This patient's confusion, miosis and lacrimation, bradycardia, diaphoresis, and bronchospasm (bilateral wheezes) indicate a state of global muscarinic **cholinergic overstimulation**. This can be the result of a pharmacologic cholinomimetic (eg, carbachol, methacholine) or **cholinesterase inhibitor** (blocks breakdown of endogenous acetylcholine).

Organophosphates are cholinesterase inhibitors that are widely used as pesticides in agriculture. They are lipid soluble; rapidly absorbed via oral, cutaneous, and inhalational routes of exposure; and readily penetrate the blood brain barrier. Organophosphates are **irreversible** cholinesterase inhibitors; they elicit cholinergic stimulation that lasts until new cholinesterase enzymes are synthesized. Organophosphate poisoning is treated with muscarinic antagonists (eg, **atropine**) and **pralidoxime** (PAM), a drug that reactivates acetylcholinesterase by binding organophosphates and decoupling them from the enzyme.

(Choices A, B, and C) Blockade of neuronal choline uptake and inhibition of choline acetyltransferase would diminish acetylcholine synthesis. Blockade of acetylcholine uptake into axoplasmic vesicles would reduce acetylcholine release from presynaptic neurons. A decrease in acetylcholine synthesis or release would have effects opposite those observed in this patient.

(Choice D) Botulinum toxin inhibits acetylcholine release from presynaptic neurons. Botulinum toxicity (botulism) causes descending skeletal muscle paralysis, typically beginning with the cranial nerves.

(Choice F) Atropine is an anticholinergic agent used pharmacologically to block post-junctional acetylcholine receptors and is the antidote for organophosphate poisoning.

Educational objective:
Organophosphates are cholinesterase inhibitors that are widely used as pesticides in agriculture. They inhibit the breakdown of acetylcholine, leading to a state of cholinergic excess. Symptoms of organophosphate poisoning include salivation, lacrimation, diaphoresis, bradycardia, and bronchospasm.

References

- Organophosphate and carbamate poisoning.

Biochemistry	Nervous System	Organophosphate poisoning
Subject	System	Topic

A 6-month-old boy is evaluated in the clinic due to delayed motor development. The mother reports that the boy is weaker than other children his age. He can barely lift his head up when prone and is unable to roll to the side. Physical examination shows generalized hypotonia and decreased deep tendon reflexes. Further evaluation reveals mutation of a protein involved in the assembly of small nuclear ribonucleoproteins (snRNPs) in motor neurons. This patient most likely has impaired function of which of the following cellular elements?

- A. Nucleosomes
- B. Peroxisomes
- C. Proteasomes
- D. Ribosomes
- E. Spliceosomes

Submit

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A. Nucleosomes (5%)
B. Peroxisomes (3%)
C. Proteasomes (4%)
D. Ribosomes (11%)
✓ E. Spliceosomes (75%)

Omitted
Correct answer
E

75%
Answered correctly

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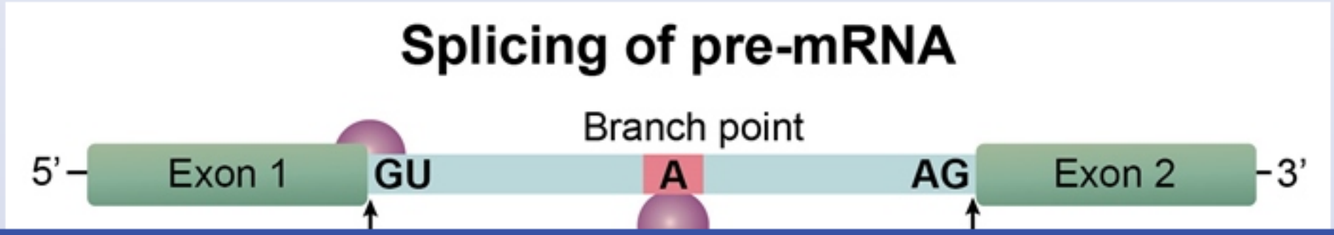
Explanation



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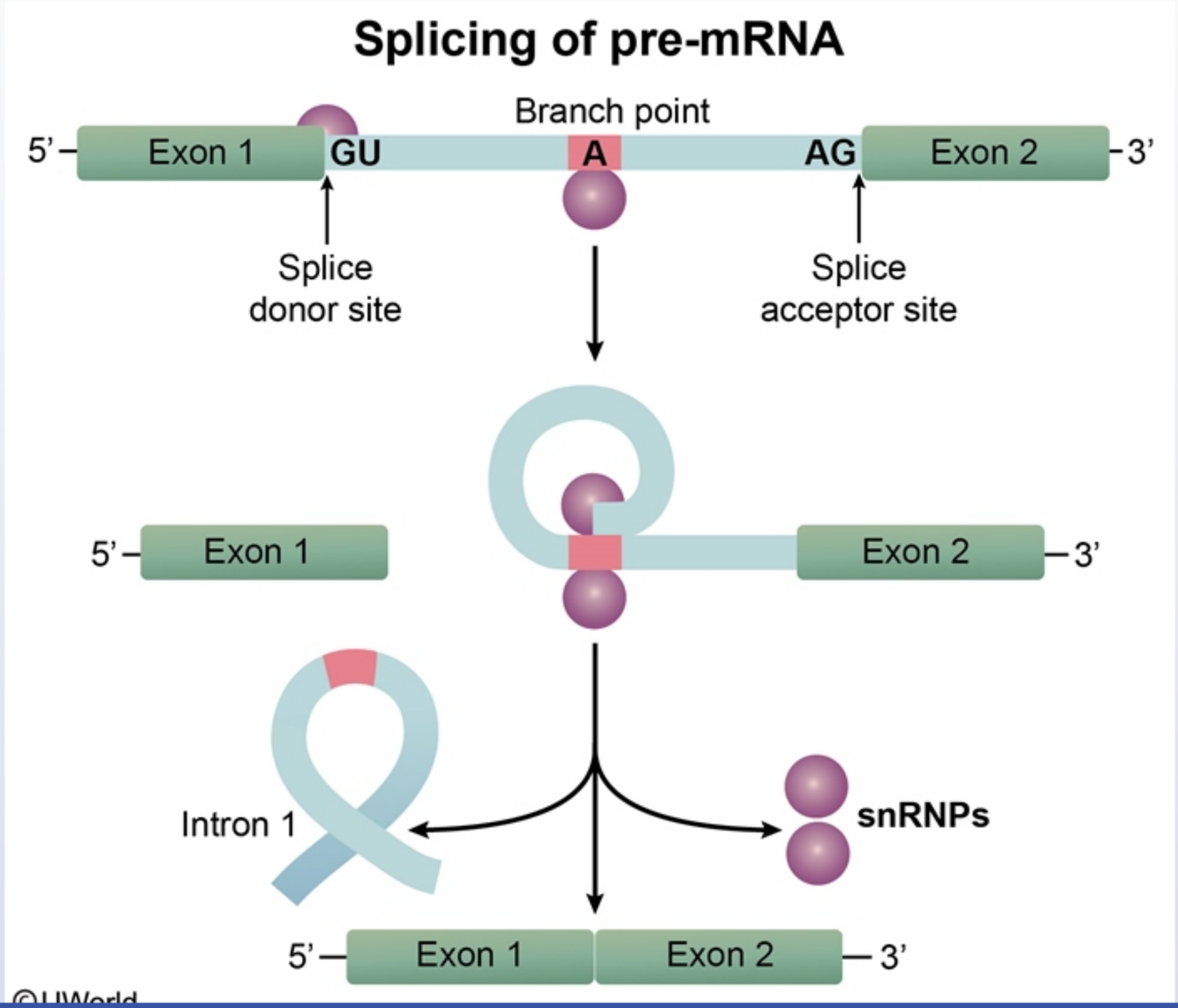

This infant with delayed motor development and flaccid paralysis (eg, hypotonia, decreased deep tendon reflexes) likely has **spinal muscular atrophy**. This condition is caused by mutations in the **survival motor neuron (*SMN1*) gene**, which encodes a protein involved in assembly of **small nuclear ribonucleoproteins (snRNPs)** in lower motor neurons. Defective snRNP assembly results in impaired spliceosome function and degeneration of anterior horn cells in the spinal cord.

RNA molecules that carry out functions without first being translated into proteins are called non-coding RNAs. These include small nuclear RNA (snRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). snRNA is transcribed by RNA polymerase II and associates with specific proteins to form snRNPs. A collection of snRNPs and other proteins on pre-mRNA is referred to as a **spliceosome**. Spliceosomes **remove introns** from pre-mRNA by cleaving the 5' end of intron 1 (splice donor site) and joining that end to the branch point. The freed 3'-OH of exon 1 then forms a phosphodiester bond with the 5'-phosphate at the splice acceptor site, joining exons 1 and 2.

(Choice A) Eukaryotic chromatin is composed of repeated subunits called nucleosomes, which consist of double-stranded DNA wrapped around histone protein cores. Nucleosomes are important for the compact packaging of DNA into chromosomes with the aid of other packaging proteins.

(Choice B) Peroxisomes are cytoplasmic organelles containing oxidative enzymes (eg, catalase, D-amino acid oxidase, uric acid oxidase). These organelles are ubiquitous among eukaryotes and are most abundant in the liver and kidneys, where detoxification of ingested and environmental materials occurs. In the liver, peroxisomes also play a role in the breakdown of fatty acids.

(Choice C) Proteasomes and lysosomes are responsible for protein/polypeptide degradation. Proteasomes mainly degrade intracellular proteins, whereas lysosomes degrade extracellular proteins and worn-out organelles.

(Choice D) Ribosomes are present in the cytoplasm and are required for translation of mRNA into protein. Individual ribosomes are comprised of rRNA and ribosomal proteins. Within the cell, rRNA engages mRNA and facilitates tRNA entry during the formation of polypeptide chains.

Educational objective:
Small nuclear ribonucleoproteins (snRNPs) are important components of the spliceosome, a molecule which removes introns from pre-mRNA during processing within the nucleus. Spinal muscular atrophy is a disorder caused by mutations in the *SMN1* gene, resulting in impaired assembly of snRNPs in lower motor neurons. Infants often have flaccid paralysis due to degeneration of anterior horn cells in the spinal cord.

References

- Spliceosome structure and function.

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References

- Spliceosome structure and function.
- Spinal muscular atrophy: a timely review.

Biochemistry	Nervous System	Spinal muscular atrophy
Subject	System	Topic

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A 4-day-old boy born to a 23-year-old woman is brought to the office for evaluation of poor feeding and vomiting. The pregnancy was uneventful and the mother had a normal delivery. Family history is noncontributory. The patient's temperature is 37.2 C (99 F), blood pressure is 60/30 mm Hg, pulse is 110/min, and respirations are 56/min. Physical examination reveals a lethargic newborn with exaggerated deep tendon reflexes and clonus. Further investigation reveals that the patient has an inherited condition that results in impaired transport of ornithine from the cytosol to the mitochondria. Nutritional restriction of which of the following substances can improve this patient's condition?

A. Branched-chain amino acids
B. Fructose
C. Galactose
D. Medium-chain triglycerides
E. Phenylalanine
F. Proteins
G. Pyridoxine

Submit

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- A. Branched-chain amino acids (18%)
- B. Fructose (2%)
- C. Galactose (2%)
- D. Medium-chain triglycerides (14%)
- E. Phenylalanine (7%)
- ✓ F. Proteins (52%)
- G. Pyridoxine (3%)

Omitted
Correct answer
F

52%
Answered correctly

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Explanation

Urea cycle

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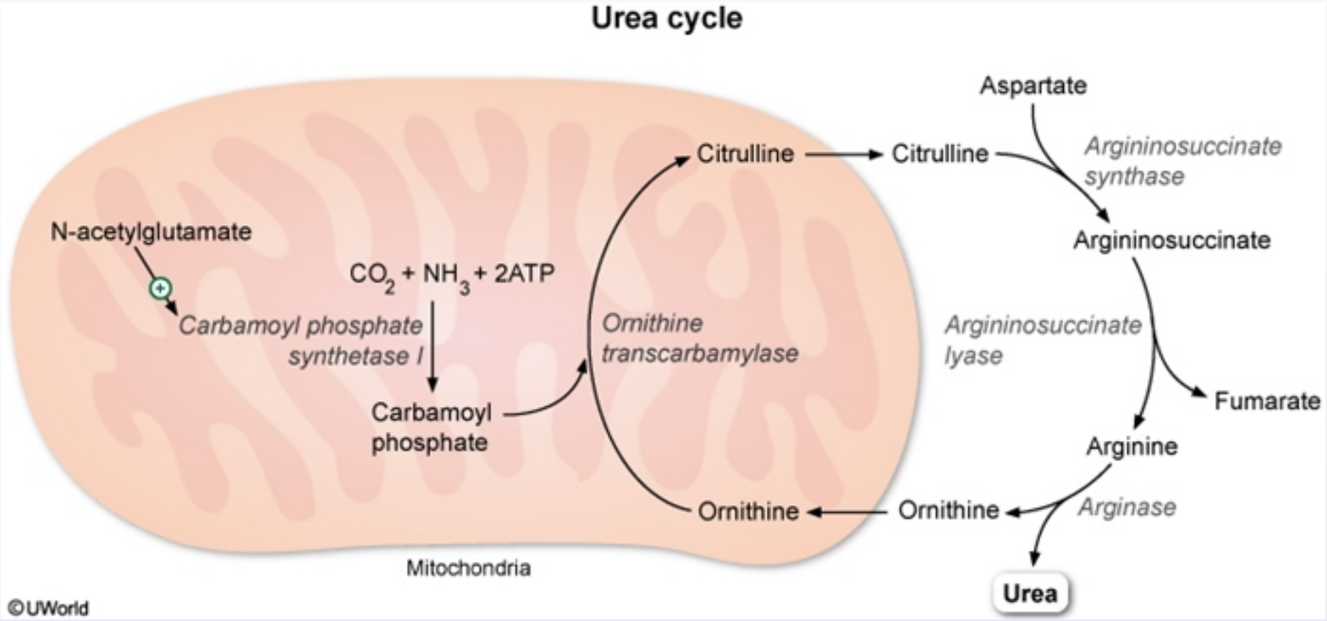

Impaired transport of ornithine into the mitochondria can be caused by ornithine translocase deficiency, which results in a defect in the **hepatic urea cycle**. The urea cycle converts ammonia, which is generated from the **catabolism of amino acids**, into urea for excretion in urine. Urea cycle **defects** cause **ammonia to accumulate** in the blood, resulting in progressive lethargy, vomiting, seizures, and cerebral edema (may cause hyperreflexia and abnormal posturing when severe) in infancy and early childhood; milder defects caused by partial enzyme deficiencies may not manifest until adulthood.

Effective treatment of urea cycle disorders requires balancing dietary protein intake and metabolic requirements. **Protein restriction** is the main treatment for urea cycle disorders, such that the body receives the essential amino acids needed for growth and development but not in excess such that excessive ammonia is formed. Medications that provide an alternate pathway to excrete nitrogen (eg, phenylacetate) are also used to help remove ammonia from the blood.

(Choice A) Restriction of branched-chain amino acids (eg, valine, leucine, isoleucine) is used to treat maple syrup urine disease (branched-chain

(Choice A) Restriction of branched-chain amino acids (eg, valine, leucine, isoleucine) is used to treat maple syrup urine disease (branched-chain alpha-ketoacid dehydrogenase deficiency) and propionic acidemia (propionyl-CoA carboxylase).

(Choice B) Fructose and sucrose restriction is the treatment for fructose 1-phosphate aldolase (aldolase B) deficiency. This condition causes vomiting and hypoglycemia in infants after fruit or juice is introduced.

(Choice C) Galactose and lactose are excluded from the diet in patients with classic galactosemia (absent galactose-1-phosphate uridyltransferase). Galactosemia presents in neonates with jaundice, vomiting, poor feeding, lethargy, hypoglycemia, and galactose-1-phosphate accumulation.

(Choice D) Medium-chain triglycerides are restricted in medium-chain acyl-CoA dehydrogenase deficiency, a condition characterized by lethargy, seizures, and hypoketotic hypoglycemia following a period of fasting.

(Choice E) A phenylalanine-free diet is recommended in patients with phenylketonuria (phenylalanine hydroxylase deficiency). Failure to convert phenylalanine to tyrosine leads to accumulation of phenylalanine and intellectual disability if the condition is left untreated.

(Choice G) Pyridoxine (vitamin B_6) can be used to treat homocystinuria, which is caused by a defect in vitamin B_6-dependent cystathionine synthase. This condition is characterized by elevated homocysteine levels, ectopia lentis, intellectual disability, Marfanoid body habitus, and increased occurrence of thromboembolic events.

Educational objective:
Ornithine transport into mitochondria is necessary for proper function of the urea cycle, which is the major disposal pathway for waste nitrogen generated by catabolism of amino acids. Urea cycle defects typically cause neurological damage due to the accumulation of ammonia. Protein restriction improves this condition by reducing the amount of amino acid turnover.

References

- The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome.

Biochemistry	Nervous System	Urea cycle
Subject	System	Topic

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A 42-year-old woman comes to the neurologist for enrollment in a research study. She has a 15-year history of resting tremor, bradykinesia, and cogwheel rigidity consistent with Parkinson's disease. One of her siblings recently started having similar symptoms. Genetic analysis is performed on the patient and her affected sibling. The results show a loss-of-function mutation in a gene that leads to an accumulation of misfolded proteins. Which of the following biochemical processes is most likely defective in this patient?

A. Acetylation
B. Gamma-carboxylation
C. Glucuronidation
D. Phosphorylation
E. Ubiquitination

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A. Acetylation (7%)
B. Gamma-carboxylation (5%)
C. Glucuronidation (2%)
D. Phosphorylation (6%)
✓ E. Ubiquitination (78%)

Omitted
Correct answer
E

78%
Answered correctly

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Explanation

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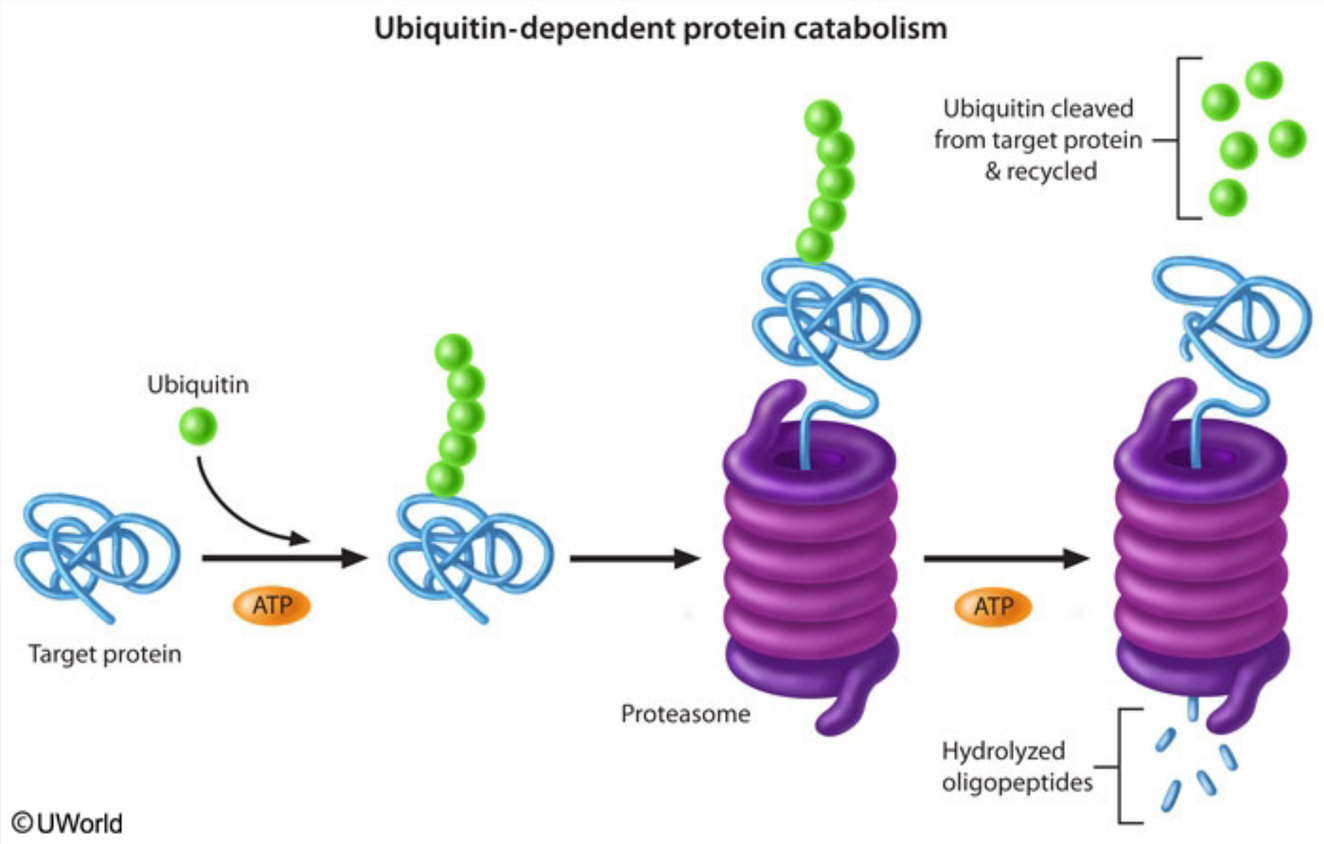

Ubiquitin is a protein found in all eukaryotic cells that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. The proteasome then recognizes these ubiquinated proteins and uses ATP energy to drive them through its tubular structure, degrading them into small peptides in the process. Attachment of 4 or more ubiquitin monomers is required before most proteins are allowed entry into the proteasome. Ubiquitination plays an important role in many cell functions, including antigen processing, muscle wasting, cell cycle regulation, DNA repair, and disposal of misfolded proteins and regulatory enzymes.

Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders such as Parkinson's and

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Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Failure of the system to properly degrade abnormal proteins causes protein misfolding, aggregation, and eventual obstruction of intracellular molecular traffic, leading to cell death. Together, the Parkin, PINK1, and DJ-1 genes code for a protein complex that promotes the degradation of misfolded proteins via the ubiquitin-proteasome system. Mutations in Parkin, PINK1, and DJ-1 are each associated with autosomal recessive forms of Parkinson's disease that have an early age of onset (< 50 years).

(Choice A) Heterochromatin is condensed and methylated DNA that has a low level of transcriptional activity. In contrast to heterochromatin, euchromatin (loosely arranged chromatin) has very high levels of transcriptional activity. Histone acetylation promotes the formation of euchromatin.

(Choice B) Vitamin K-dependent gamma-carboxylation is critical for the functioning of clotting factors II, VII, IX, and X, and of the anticoagulative proteins C and S. Warfarin inhibits carboxylation of these proteins.

(Choice C) The hepatic processing of bilirubin is accomplished in three key steps: carrier-mediated passive uptake of bilirubin at the sinusoidal membrane; conjugation of bilirubin with glucuronic acid in the endoplasmic reticulum; and active biliary excretion of the water-soluble, nontoxic bilirubin-glucuronides. Disruption of this process occurs in Crigler-Najjar syndrome, a condition in which patients lack the enzyme needed to catalyze bilirubin glucuronidation.

(Choice D) Phosphorylation is the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule. Phosphorylation is commonly involved in the regulation of enzymatic activity.

Educational objective:
Ubiquitin is a protein that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. These modified proteins enter the proteasome and are degraded into small peptides. Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders, including Parkinson's and Alzheimer's diseases.

with autosomal recessive forms of Parkinson's disease that have an early age of onset (<50 years).

(Choice A) Heterochromatin is condensed and methylated DNA that has a low level of transcriptional activity. In contrast to heterochromatin, euchromatin (loosely arranged chromatin) has very high levels of transcriptional activity. Histone acetylation promotes the formation of euchromatin.

(Choice B) Vitamin K-dependent gamma-carboxylation is critical for the functioning of clotting factors II, VII, IX, and X, and of the anticoagulative proteins C and S. Warfarin inhibits carboxylation of these proteins.

(Choice C) The hepatic processing of bilirubin is accomplished in three key steps: carrier-mediated passive uptake of bilirubin at the sinusoidal membrane; conjugation of bilirubin with glucuronic acid in the endoplasmic reticulum; and active biliary excretion of the water-soluble, nontoxic bilirubin-glucuronides. Disruption of this process occurs in Crigler-Najjar syndrome, a condition in which patients lack the enzyme needed to catalyze bilirubin glucuronidation.

(Choice D) Phosphorylation is the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule. Phosphorylation is commonly involved in the regulation of enzymatic activity.

Educational objective:
Ubiquitin is a protein that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. These modified proteins enter the proteasome and are degraded into small peptides. Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders, including Parkinson's and Alzheimer's diseases.

References

- Parkin and defective ubiquitination in Parkinson's disease.
- Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation.

Biochemistry	Nervous System	Ubiquitin proteasome pathway
Subject	System	Topic

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A 24-year-old woman comes to the office due to a persistent facial rash. The patient easily develops "sunburns" after sun exposure and her fingers "turn blue" in cold weather. She has also felt more fatigued than usual. Physical examination shows a facial rash in a butterfly distribution that spares the nasolabial folds. Laboratory studies reveal several types of autoantibodies directed against components of the cell nucleus. One specific antibody targets proteins complexed with small nuclear ribonucleic acid. These protein-ribonucleic acid complexes are most likely involved in which of the following cellular functions?

A. Aiding mRNA in exiting the nucleus
B. Allowing proper functioning of DNA ligase
C. Charging tRNA with amino acids
D. Polyadenylation of RNA transcripts
E. Removal of introns from RNA transcripts
F. Synthesizing Okazaki fragments

Submit

A 24-year-old woman comes to the office due to a persistent facial rash. The patient easily develops "sunburns" after sun exposure and her fingers "turn blue" in cold weather. She has also felt more fatigued than usual. Physical examination shows a facial rash in a butterfly distribution that spares the nasolabial folds. Laboratory studies reveal several types of autoantibodies directed against components of the cell nucleus. One specific antibody targets proteins complexed with small nuclear ribonucleic acid. These protein-ribonucleic acid complexes are most likely involved in which of the following cellular functions?

- A. Aiding mRNA in exiting the nucleus (12%)
- B. Allowing proper functioning of DNA ligase (5%)
- C. Charging tRNA with amino acids (8%)
- D. Polyadenylation of RNA transcripts (5%)
- ✓ E. Removal of introns from RNA transcripts (64%)
- F. Synthesizing Okazaki fragments (3%)

Omitted
Correct answer
E

64%
Answered correctly

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01/29/2020
Last Updated

Explanation

Splicing of pre-mRNA

Branch point

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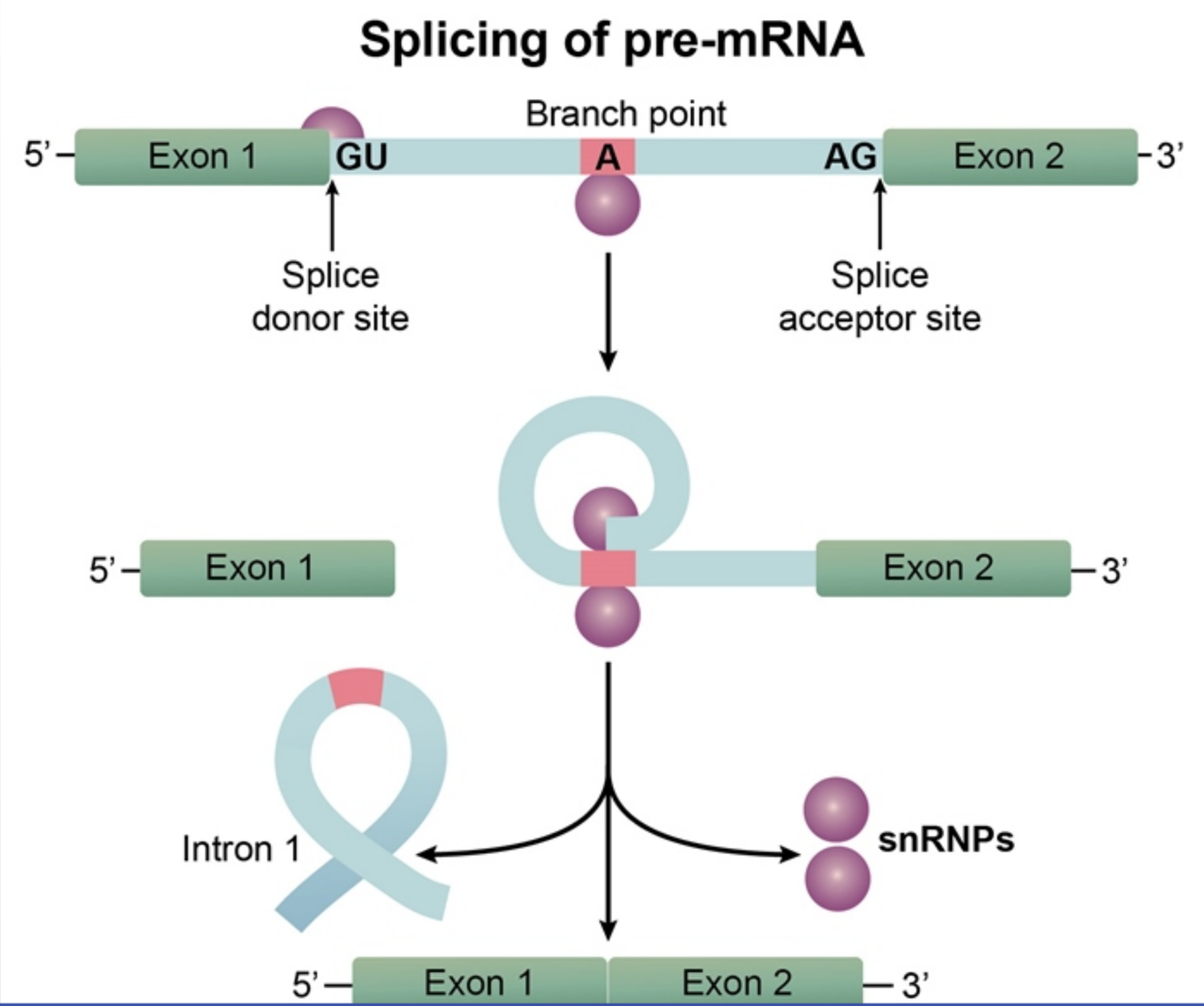

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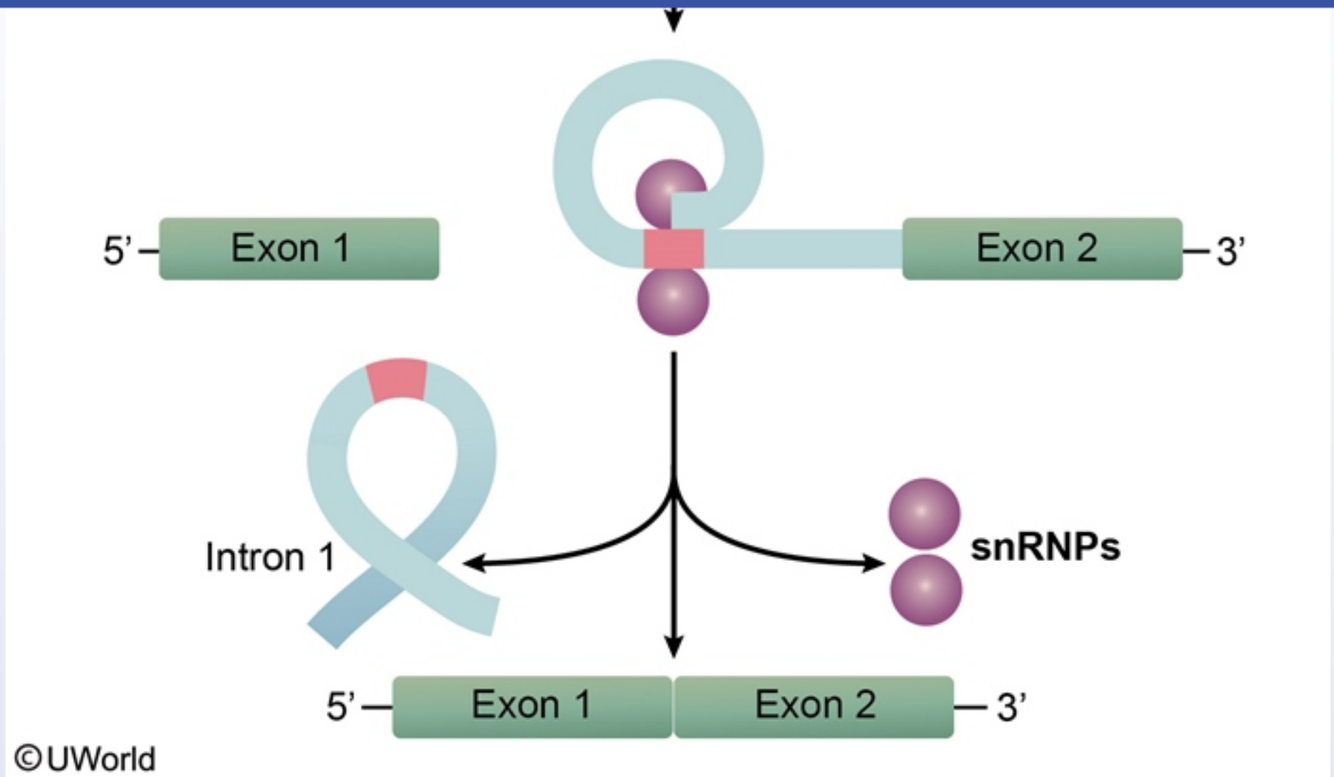

This patient's constellation of symptoms (eg, malar rash, photosensitivity, Raynaud phenomenon ["blue fingers"], fatigue) is consistent with systemic lupus erythematosus, an autoimmune disease associated with anti-Smith antibodies (highly specific). Smith protein normally complexes with small nuclear RNA (snRNA) in the cytoplasm, forming small nuclear ribonucleoproteins (snRNPs).

Transcription occurs in the nucleus and is catalyzed by 3 types of RNA polymerases, leading to the formation of messenger RNA (mRNA), ribosomal RNA (rRNA), transport RNA (tRNA), and snRNA. **RNA polymerase II** synthesizes both mRNA and **snRNA**, the latter of which combines with specific proteins to form **snRNPs**. mRNA synthesis occurs in 2 stages. During the first, the DNA template is transcribed into a complementary strand of pre-mRNA. In the second, pre-mRNA is processed into mature mRNA through the following steps:

1. RNA capping: Addition of a methylated guanine nucleotide to the 5' end.

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1. RNA capping: Addition of a methylated guanine nucleotide to the 5' end.
2. RNA polyadenylation: Addition of several adenine nucleotides to the 3' end (poly-A tail).
3. RNA splicing: **Removal of introns** (noncoding regions) by **spliceosomes**, which consist of snRNPs and other proteins.

Mature mRNA then transfers the genetic code to the cytoplasm and serves as a template for protein synthesis (translation).

(Choices A and D) Polyadenylation of RNA transcripts is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA, helping it exit the nucleus.

(Choices B and F) During eukaryotic DNA replication, DNA polymerase δ elongates Okazaki fragments of the lagging strand. These Okazaki fragments are later joined by the enzyme DNA ligase.

(Choice C) During translation, aminoacyl-tRNA synthetases catalyze the linkage of tRNAs to their corresponding amino acids. Each enzyme recognizes a specific amino acid and all of the tRNAs that match that amino acid.

Educational objective:
Small nuclear RNA (snRNA) is synthesized by RNA polymerase II in the nucleus and complexes with specific proteins to form small nuclear ribonucleoproteins (snRNPs). snRNPs are an essential component of spliceosomes, which remove introns from pre-mRNA to form mature mRNA. Patients with systemic lupus erythematosus can have autoantibodies directed against snRNPs (eg, anti-Smith antibody).

References

- Spliceosome structure and function.

complementary strand of pre-mRNA. In the second, pre-mRNA is processed into mature mRNA through the following steps:

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Educational objective:
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References

- Spliceosome structure and function.
- Anti-Sm and anti-RNP antibodies.

Biochemistry	Rheumatology/Orthopedics & Sports	Splice site mutation
Subject	System	Topic

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A 2-year-old boy is brought to the office by his parents. He is currently toilet-training during the day and at nighttime. After he urinated in the toilet last night, his parents forgot to flush the toilet and noticed that the boy's urine turned black overnight. The child has no significant past medical history and takes no medications. He can say 2-word sentences, follow 2-step directions, and jump with 2 feet off the ground. Examination shows a well-nourished child with no swelling or tenderness of any joints. Urinalysis results are as follows:

Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

A. Leucine to acetoacetate
B. Phenylalanine to tyrosine
C. Serine to cysteine
D. Tyrosine to fumarate
E. Valine to glutamic acid

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Color	black
Specific gravity	1.022
Protein	none
Blood	negative
Glucose	negative
Ketones	negative
Leukocyte esterase	negative

Which of the following conversion pathways is most likely deficient in this patient?

A. Leucine to acetoacetate (6%)
B. Phenylalanine to tyrosine (19%)
C. Serine to cysteine (15%)
✓ D. Tyrosine to fumarate (54%)
E. Valine to glutamic acid (3%)

Omitted
Correct answer

54%
Answered correctly

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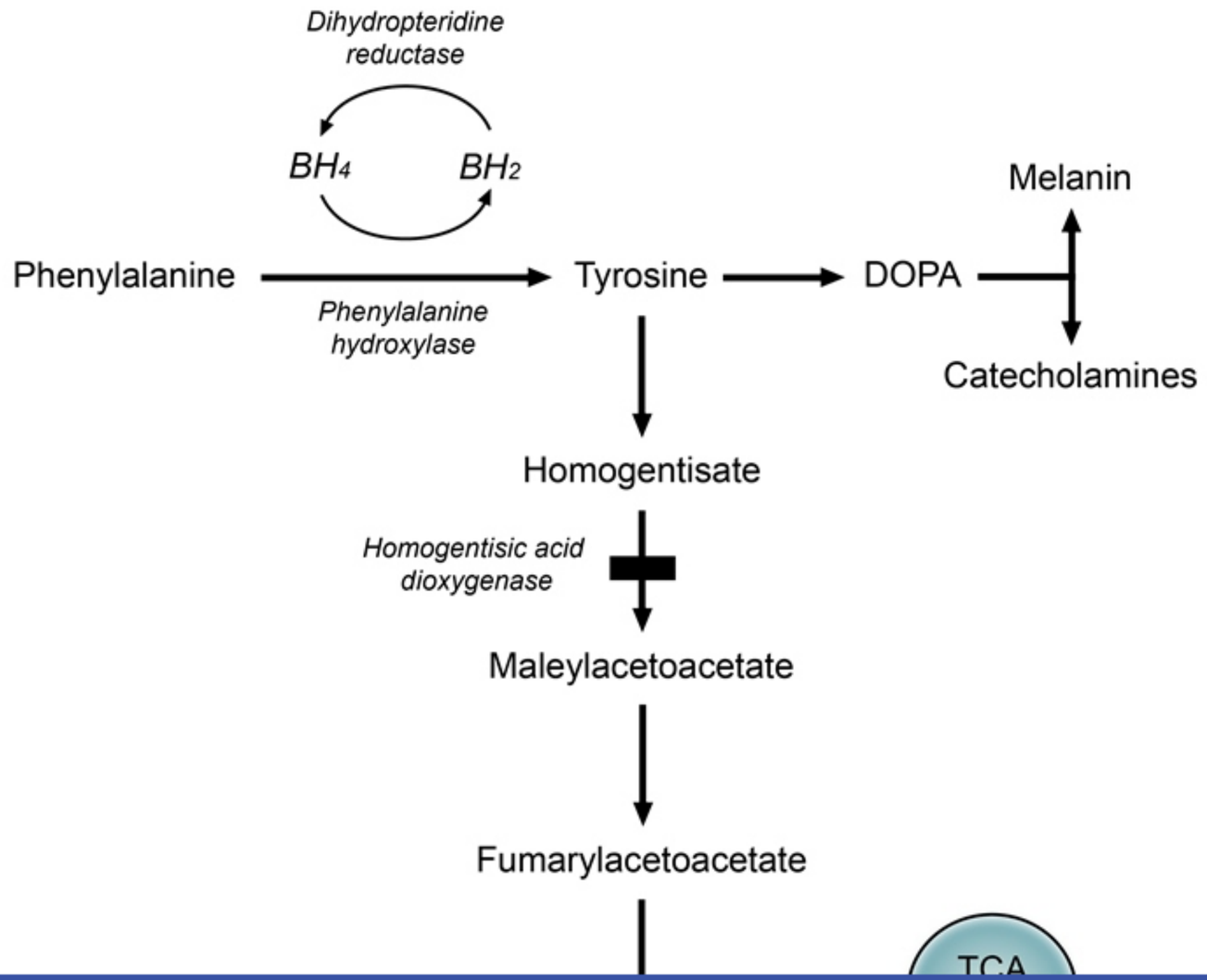
Alkaptonuria



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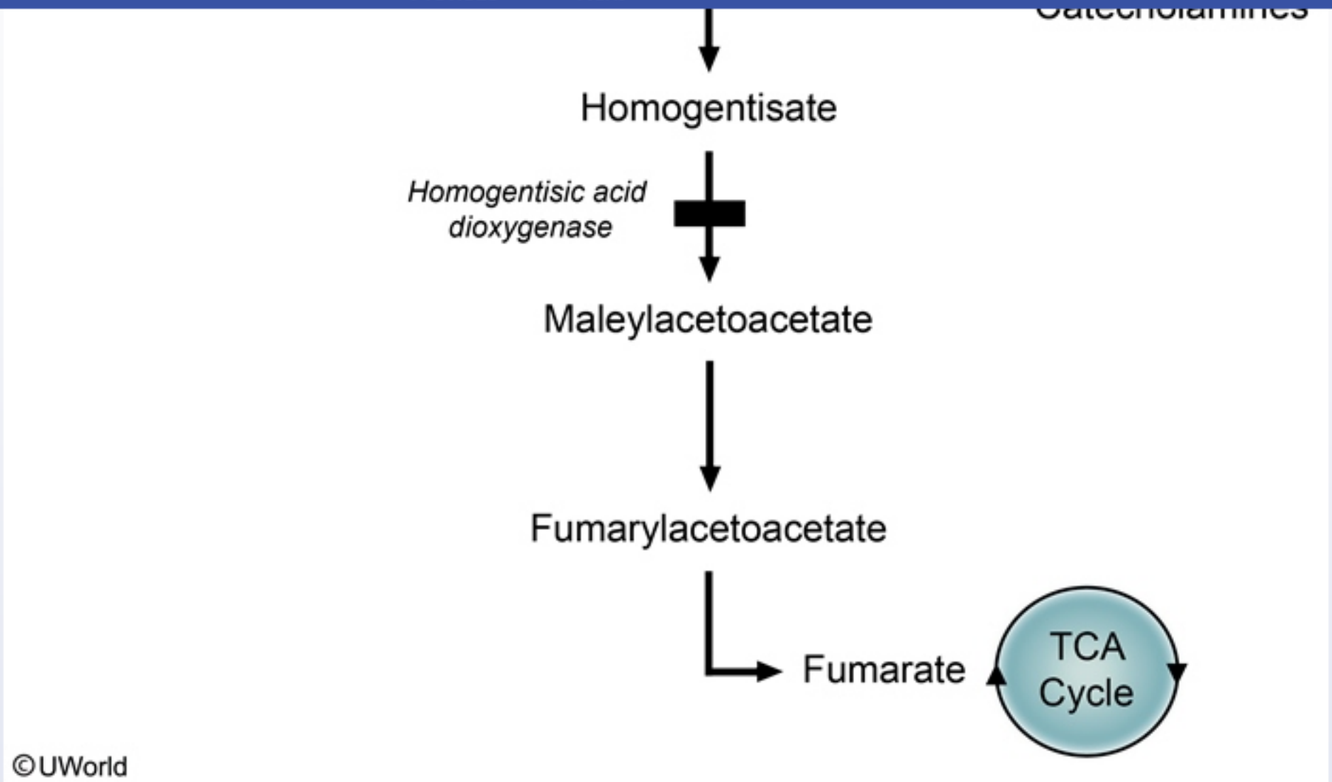

Alkaptonuria is an **autosomal recessive** disorder of **tyrosine metabolism**. Deficiency of homogentisic acid dioxygenase blocks homogentisic acid metabolism, preventing the conversion of tyrosine to fumarate. Homogentisic acid accumulates in the body and is excreted in the urine, imparting a **black color** to the **urine** if allowed to sit and undergo oxidation. In patients with alkaptonuria, the retained homogentisic acid selectively binds to collagen in connective tissues, tendons, and cartilage. This leads to "**ochronosis**," a blue-black pigmentation most evident in the ears, nose, and cheeks, and **ochronotic arthropathy**, which typically manifests during adulthood.

(Choice A) Leucine is a branched-chain amino acid that is elevated in maple syrup urine disease. Isoleucine and valine are also increased. Impaired metabolism of these amino acids leads to cerebral edema, seizures, and a sweet smell of the urine.

(Choice B) Conversion of phenylalanine to tyrosine is defective in phenylketonuria and usually occurs due to a defect in phenylalanine

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(Choice A) Leucine is a branched-chain amino acid that is elevated in maple syrup urine disease. Isoleucine and valine are also increased. Impaired metabolism of these amino acids leads to cerebral edema, seizures, and a sweet smell of the urine.

(Choice B) Conversion of phenylalanine to tyrosine is defective in phenylketonuria and usually occurs due to a defect in phenylalanine hydroxylase. Undiagnosed and untreated phenylketonuria results in significant intellectual disability not seen in this patient.

(Choice C) Impaired renal cystine (a homodimer of cysteine) transport leads to cystinuria, a disease characterized by flank pain, hematuria, and renal stones in childhood or adolescence.

(Choice E) Sickle cell anemia results from the substitution of valine for glutamic acid due to a single-nucleotide polymorphism. This mutation leads to loss of red cell elasticity, polymerization of sickle hemoglobin, and sickling of red blood cells, which results in vasoocclusive crises.

Educational objective:
Alkaptonuria is an autosomal recessive disorder in which the lack of homogentisic acid dioxygenase blocks the metabolism of tyrosine, leading to an accumulation of homogentisic acid. Clinical features include a black urine color when exposed to air, a blue-black pigmentation on the face, and ochronotic arthropathy.

References

- Alkaptonuria.

Biochemistry	Miscellaneous (Multisystem)	Alkaptonuria
Subject	System	Topic

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As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

A. α-Ketoglutarate

B. L-citrulline

C. Malate

D. Citrate

E. Oxaloacetate

Submit

As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

- ✓ A. α-Ketoglutarate (61%)
- B. L-citrulline (5%)
- C. Malate (7%)
- D. Citrate (5%)
- E. Oxaloacetate (19%)

Omitted
Correct answer
A

61%
Answered correctly

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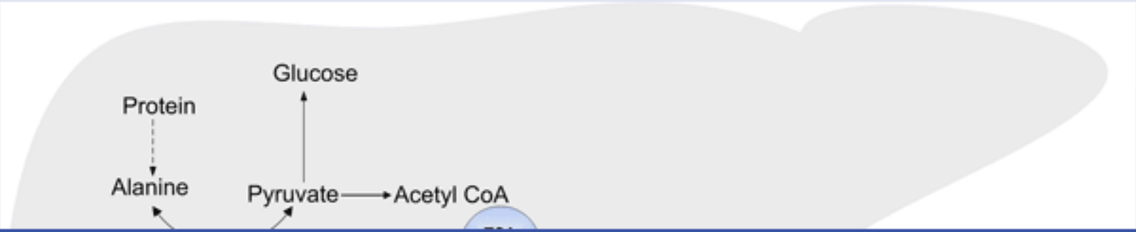
Explanation



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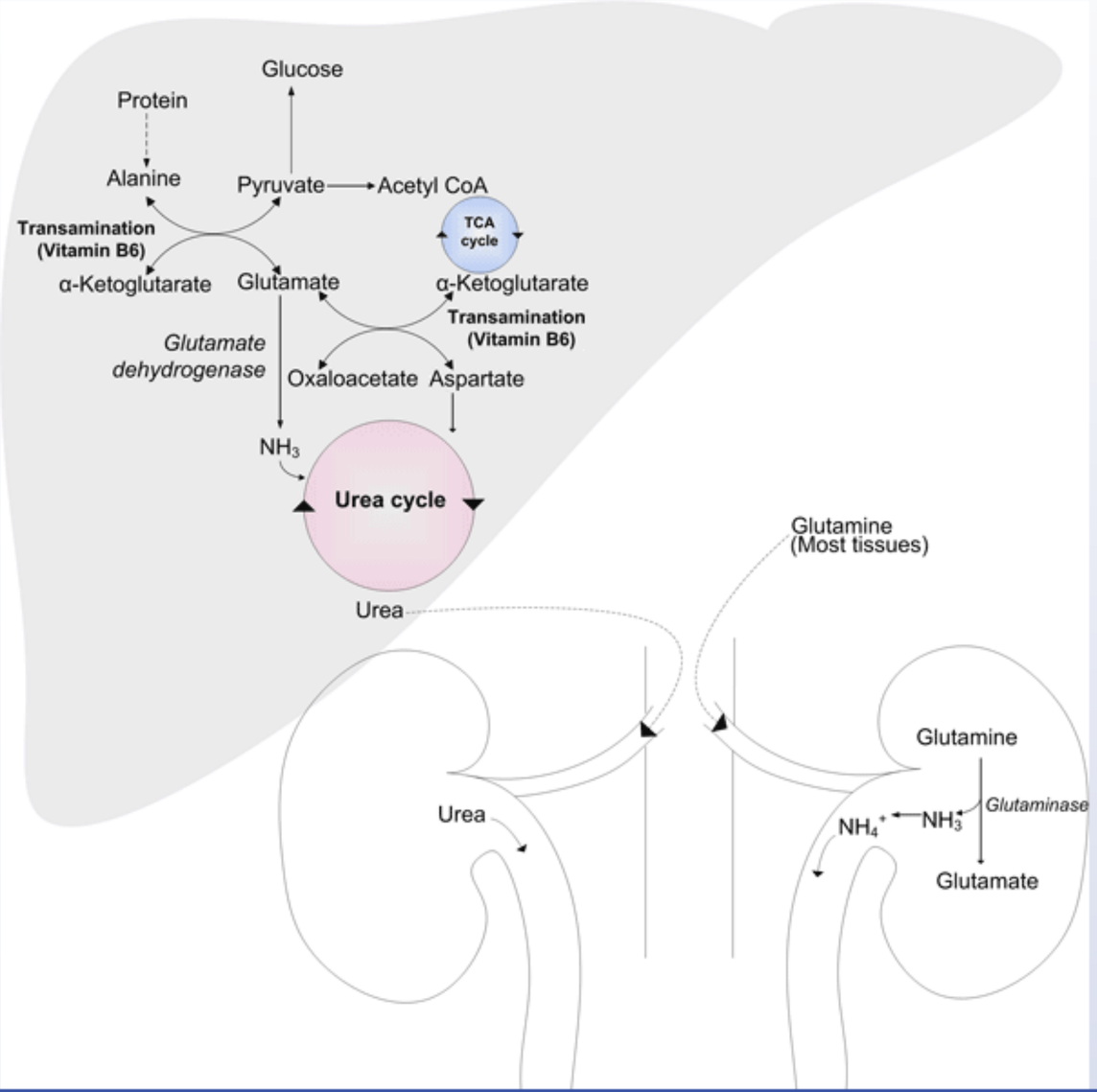

Alanine and glutamine play an important role in transporting nitrogen throughout the body. Glutamine is produced by most body tissues and is catabolized primarily by the gut and kidney for maintenance of cellular metabolism and acid-base regulation, respectively. A significant portion of the glutamine used by these tissues is converted to alanine and released into the circulation. Alanine is also released by skeletal muscle tissue during protein catabolism as part of the glucose-alanine cycle that helps remove excess nitrogen. Alanine is then transported to the liver, where it serves as a vehicle for nitrogen disposal and as a source of carbon skeletons for gluconeogenesis.

In the liver, alanine is transaminated by alanine aminotransferase to pyruvate with the amino group being transferred to α-ketoglutarate to form glutamate. Almost all aminotransferase enzymes use α-ketoglutarate as the amino group acceptor. Thus, amino groups are funneled into glutamate during protein catabolism. Glutamate is further metabolized by the enzyme glutamate dehydrogenase, which liberates free ammonia and regenerates α-ketoglutarate. Ammonia then enters the urea cycle to form urea, the primary disposal form of nitrogen in humans. Urea subsequently enters the blood and is excreted in the urine.

(Choices C, D, and E) Malate, citrate, and oxaloacetate are all intermediates of the tricarboxylic acid cycle.

(Choice B) L-citrulline is an amino acid produced as an intermediate in the conversion of ornithine to argininosuccinate during the hepatic urea cycle.

Educational objective:
Alanine is the major amino acid responsible for transferring nitrogen to the liver for disposal. During the catabolism of proteins, amino groups are transferred to α-ketoglutarate to form glutamate. Glutamate is then processed in the liver to form urea, the primary disposal form of nitrogen in humans. Free ammonia is also excreted into the urine by the kidney for regulation of acid-base status.

Biochemistry	Nervous System	Tca cycle
Subject	System	Topic

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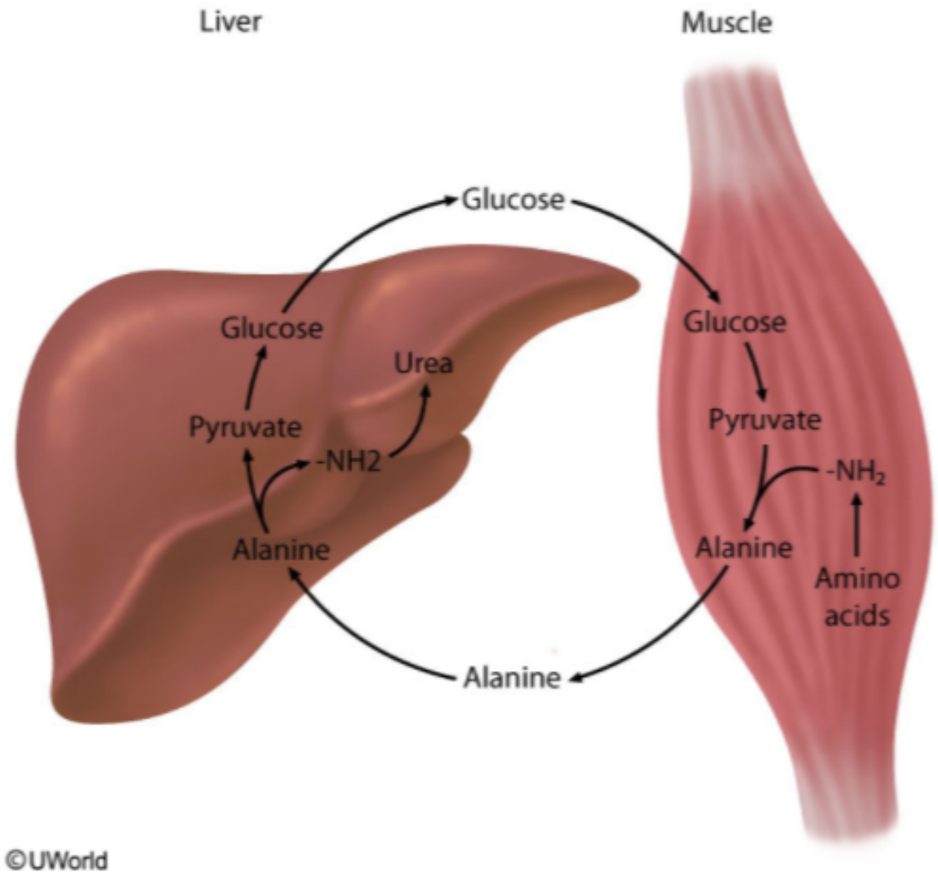

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A 44-year-old man is evaluated due to progressive dyspnea over the past several years. The patient has no associated chest pain or palpitations. Physical examination shows a prolonged expiratory phase without wheezes or rhonchi. CT scan of the chest demonstrates bilateral lower lobe–predominant emphysema. Further testing reveals that the patient has a protease inhibitor deficiency, which has led to increased elastin fiber breakdown. Elastin fibers within alveolar walls normally allow the lung to stretch during active inspiration and recoil during passive expiration. Which of the following most likely contributes to this property of elastin?

A. Abundant interchain disulfide bridges
B. Chain assembly to form a triple helix
C. Heavy post-translational hydroxylation
D. High content of polar amino acids
E. Interchain cross-links involving lysine

Submit

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- A. Abundant interchain disulfide bridges (23%)
- B. Chain assembly to form a triple helix (14%)
- C. Heavy post-translational hydroxylation (8%)
- D. High content of polar amino acids (7%)
- ✓ E. Interchain cross-links involving lysine (45%)

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Correct answer
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45%
Answered correctly

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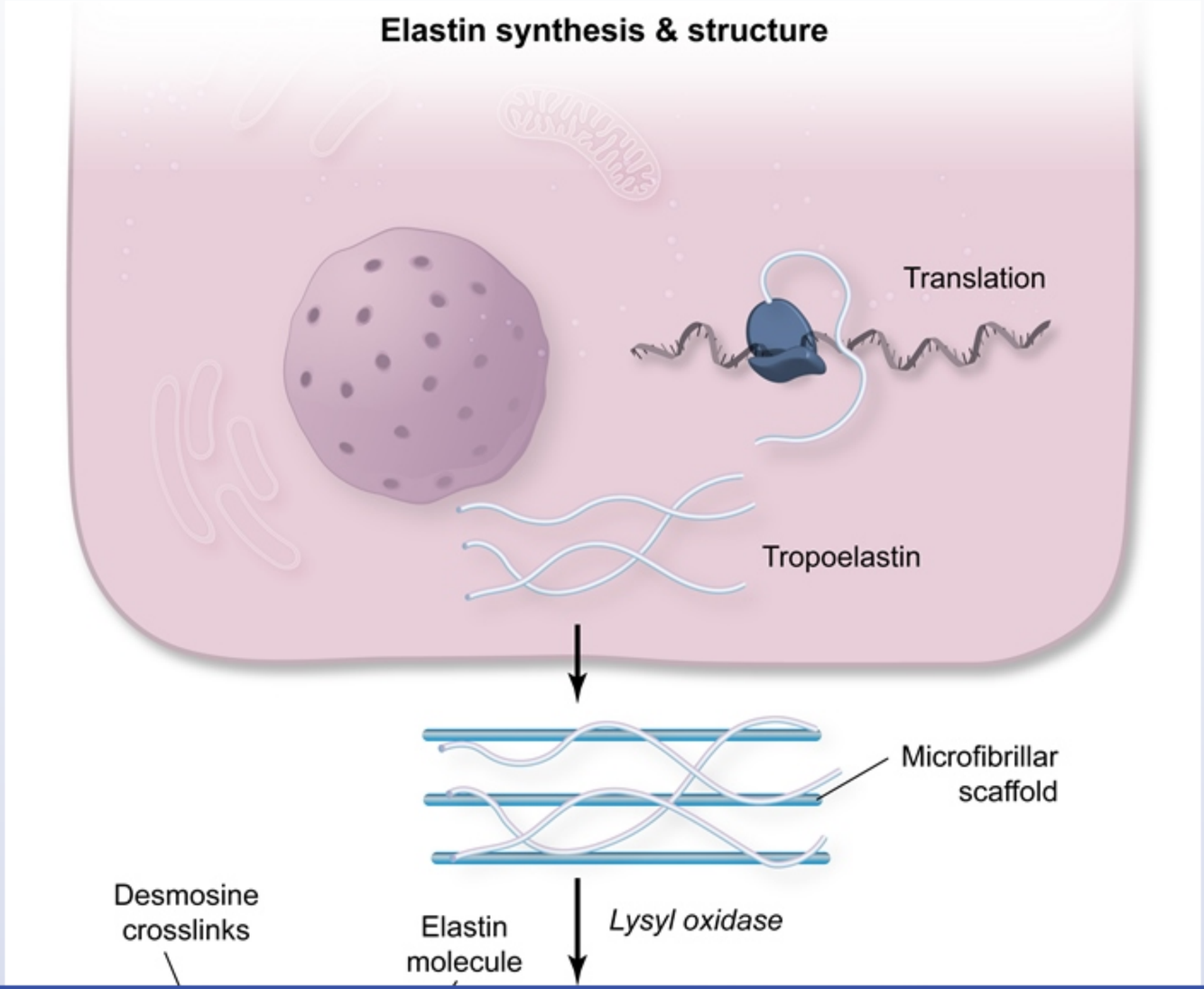
Last Updated

Explanation

Explanation



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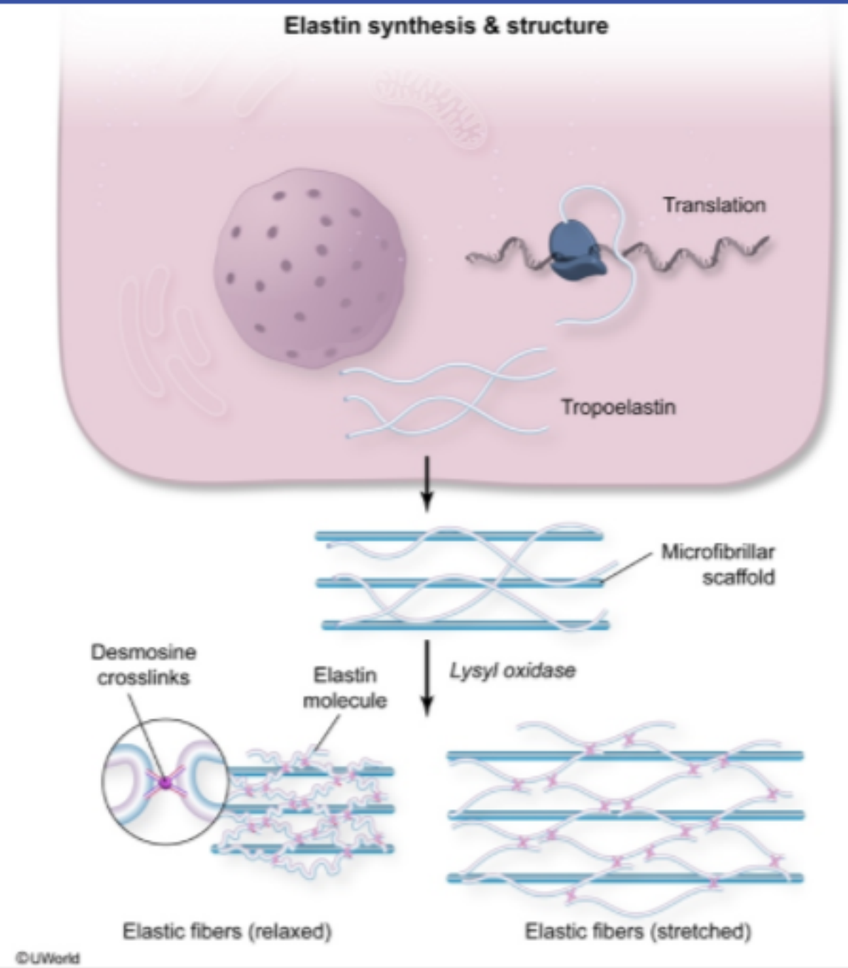

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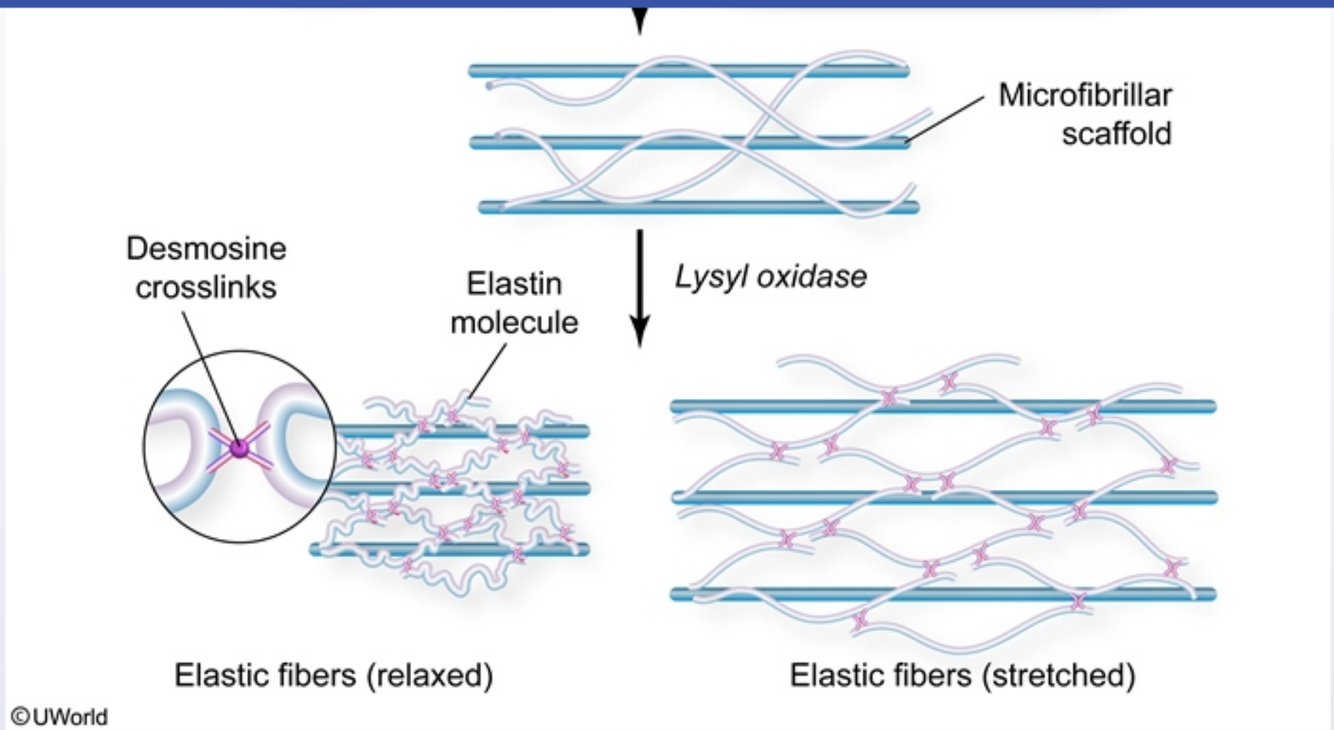

This patient's emphysema is likely due to **alpha-1 antitrypsin deficiency**. Neutrophil-secreted elastase is an endogenous proteolytic enzyme that hydrolyzes elastin within alveolar walls. The liver synthesizes alpha-1 antitrypsin, a protein that inhibits neutrophil elastase and prevents alveolar wall degradation, particularly in the lower airways. Patients with alpha-1 antitrypsin deficiency consequently develop excessive alveolar **elastin degradation**, which clinically manifests with **early-onset**, lower lobe–predominant emphysema.

Elastin is a fibrous connective tissue protein that provides elasticity to the skin, blood vessels, and pulmonary alveoli. The fibers can stretch to several times their length and recoil back to their original size once stretching forces are withdrawn. Elastin assembly is closely related to that of collagen. Similar to collagen, elastin is synthesized as a large polypeptide precursor (tropoelastin) composed of about 700, mostly nonpolar, amino acids (eg, glycine, alanine, valine) **(Choice D)**. Elastin also contains proline and lysine residues; however, in contrast to those found in collagen, few of these amino acids are hydroxylated **(Choice C)**.

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After tropoelastin is formed, it is secreted into the extracellular space where it interacts with microfibrils (fibrillin) that function as a scaffold. Next, **lysyl oxidase**, a copper-dependent enzyme, oxidatively deaminates some of the lysine residues of tropoelastin, facilitating the formation of **desmosine cross-links** between neighboring polypeptides that hold the elastin molecules together. These cross-links, along with the high content of nonpolar (hydrophobic) amino acids, account for the **rubber-like properties** of elastin.

(Choices A and B) Disulfide bridges are formed during collagen, not elastin, synthesis. After post-translational hydroxylation and glycosylation of procollagen molecules, disulfide bond formation between the C-terminal propeptide regions of 3 alpha chains brings the chains into a favorable alignment for triple helix assembly.

Educational objective:
The rubber-like properties of elastin are due to high content of nonpolar (hydrophobic) amino acids and extensive cross-linking between elastin monomers facilitated by lysyl oxidase. Patients with alpha-1 antitrypsin deficiency can develop early-onset, lower lobe–predominant emphysema due to excessive alveolar elastin degradation.

References

- Elastin metabolism and chemistry: potential roles in lung development and structure.

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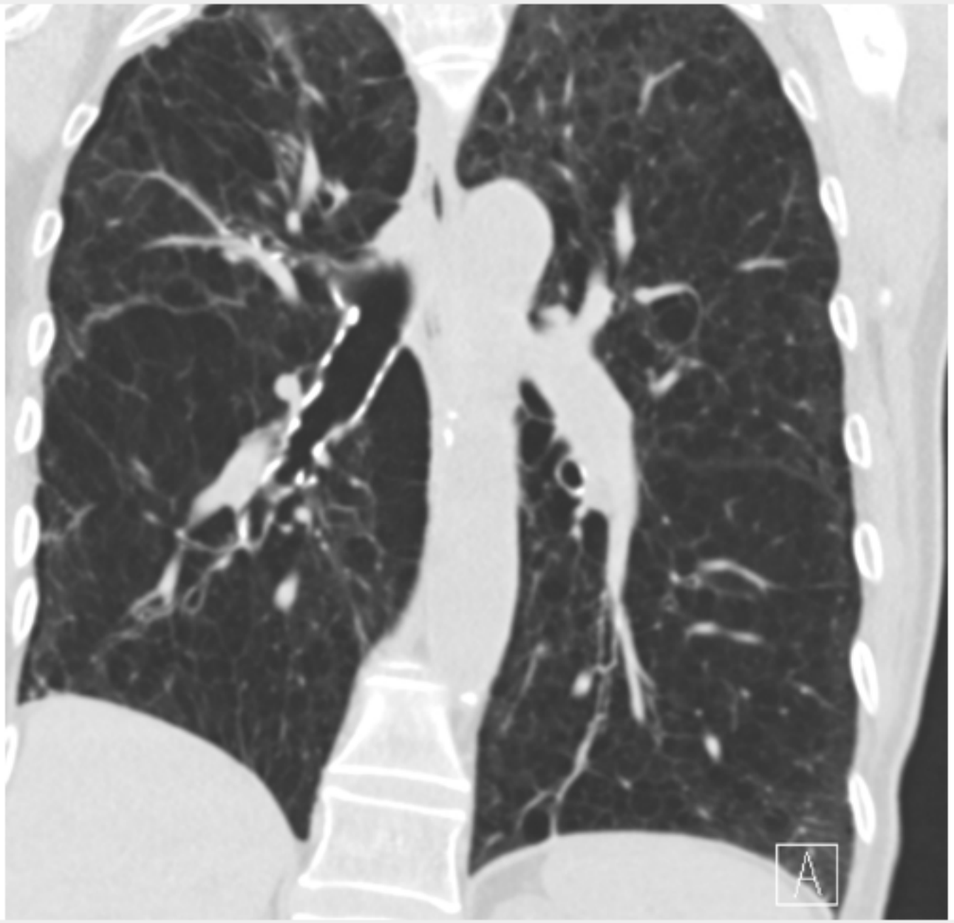
Alpha-1-antitrypsin deficiency Alpha-1-antitrypsin deficiency



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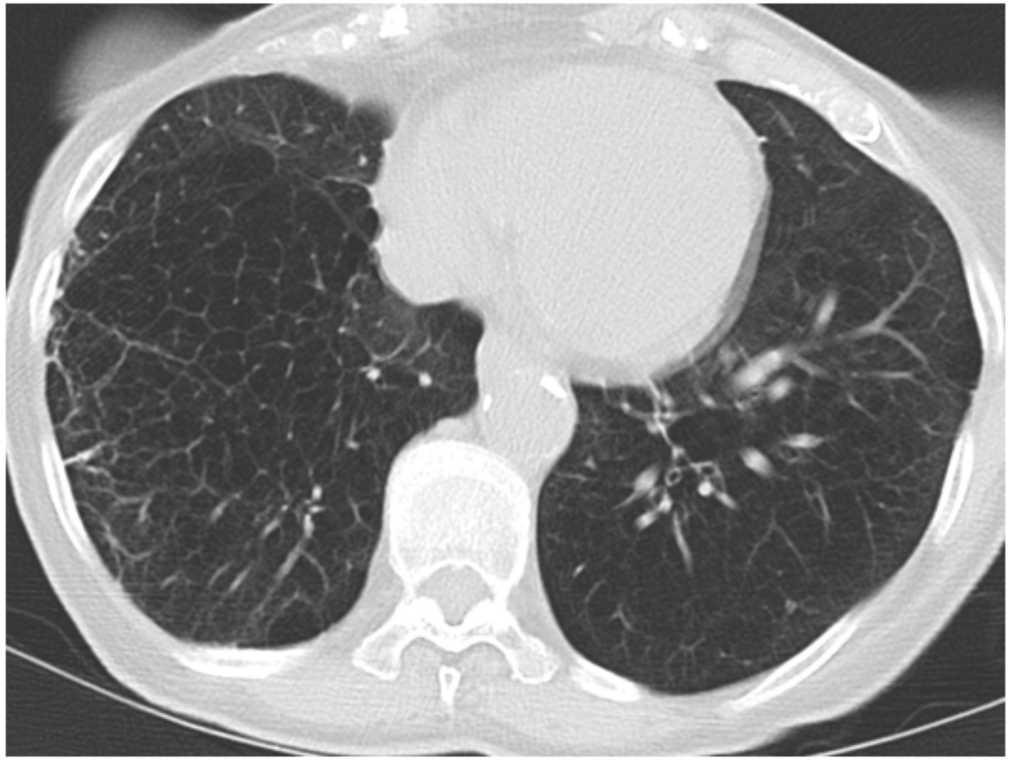
Alpha-1-antitrypsin deficiency Alpha-1-antitrypsin deficiency



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A 5-month-old boy is brought to the office by his parents who are concerned that he has developmental delay. He has 3 older siblings, and the parents report that his siblings were much more active and interactive at the boy's age. The family has just moved to the United States from South America and did not have consistent primary care previously. Physical examination shows that the boy is unable to roll from front to back or back to front and does not seem to recognize his parents. Comprehensive laboratory evaluation reveals impaired tetrahydrobiopterin synthesis. Which of the following is most likely deficient in this patient?

A. Acetylcholine
B. Gamma-aminobutyric acid
C. Glutamate
D. Phenylalanine
E. Serotonin

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A. Acetylcholine (6%)
B. Gamma-aminobutyric acid (10%)
C. Glutamate (14%)
D. Phenylalanine (30%)
✓ E. Serotonin (37%)

Omitted
Correct answer
E

37%
Answered correctly

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Time Spent

03/08/2020
Last Updated

Explanation

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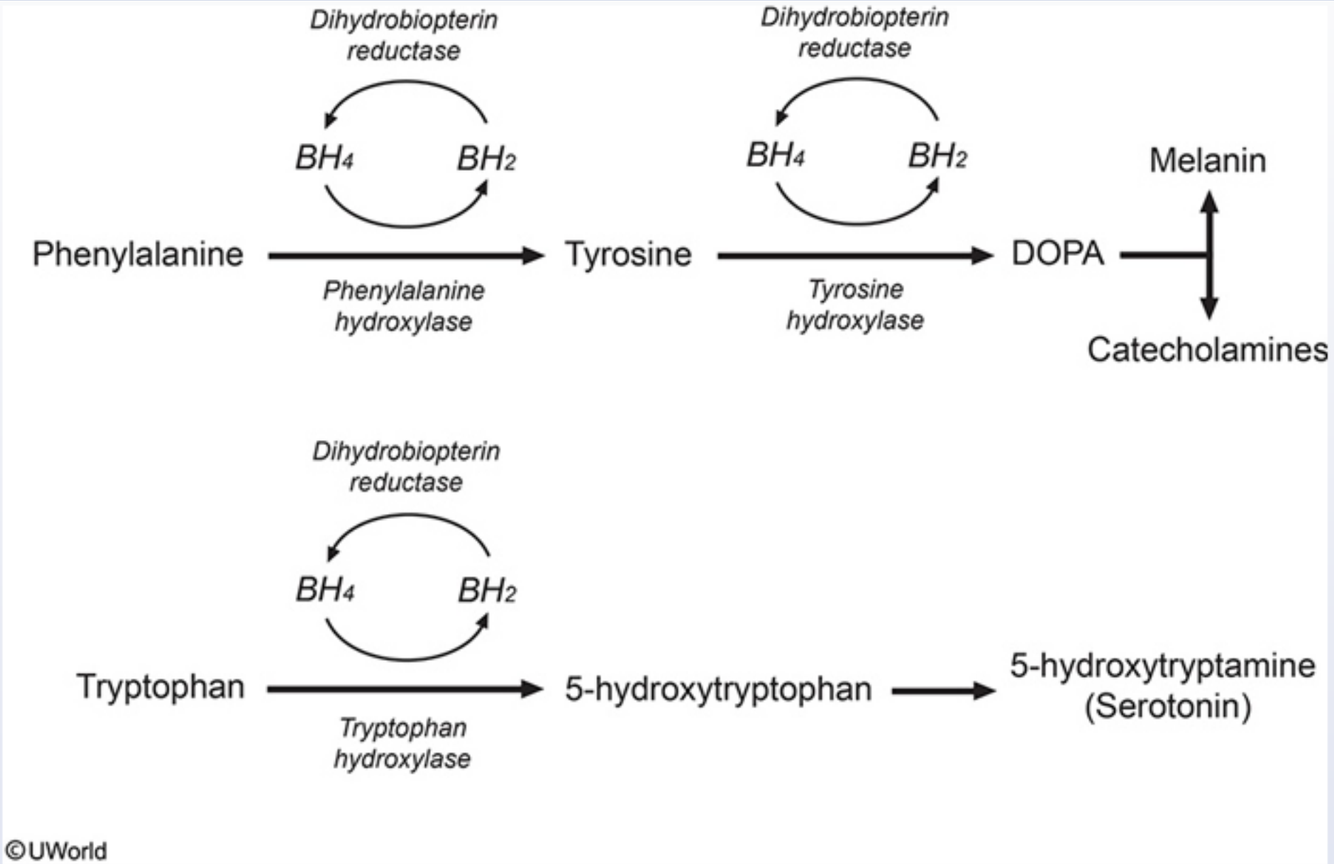

Tetrahydrobiopterin (BH_4) is a cofactor in the synthesis of serotonin (a major neurotransmitter), tyrosine (a precursor of DOPA), and DOPA (the antecedent of the neurotransmitters dopamine, norepinephrine and epinephrine). Dihydropteridine reductase enzymatically reduces dihydrobiopterin (BH_2) to tetrahydrobiopterin (BH_4). Serotonin (5-hydroxytryptamine, or 5HT) is formed through hydroxylation and decarboxylation of the amino acid tryptophan.

Most cases of **phenylketonuria** are due to phenylalanine hydroxylase deficiency. Less commonly, the etiology is due to **BH_4 deficiency** secondary to **dihydropteridine reductase deficiency**. The consequences of defective phenylalanine and tryptophan metabolism are

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Most cases of **phenylketonuria** are due to phenylalanine hydroxylase deficiency. Less commonly, the etiology is due to **BH_4 deficiency** secondary to **dihydropteridine reductase deficiency**. The consequences of defective phenylalanine and tryptophan metabolism are phenylalanine accumulation **(Choice D)** and **low levels of serotonin and other neurotransmitters**, respectively.

The combination of high phenylalanine levels, which may disrupt neuronal and glial development, and low serotonin and other neurotransmitters results in progressive **neurologic deterioration** in untreated patients. Manifestations include developmental delay, hypotonia, dystonia, and seizures. Treatment includes both a **low phenylalanine diet** and **BH_4 supplementation**.

(Choice A) Acetylcholine is a neuromuscular junction neurotransmitter synthesized from choline and acetyl-CoA by choline acetyltransferase. In myasthenia gravis, production of antibodies against acetylcholine receptors leads to muscle weakness.

(Choice B) Gamma-aminobutyric acid (GABA) is an inhibitor of presynaptic transmission in the central nervous system that is formed by glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase. Phenobarbital, an antiepileptic medication, potentiates GABA activity to decrease or cease seizure activity.

(Choice C) Glutamate is an excitatory neurotransmitter that is synthesized from glutamine by the enzyme glutaminase. Ketamine is an N-methyl-D-aspartate (NMDA) receptor noncompetitive antagonist that blocks glutamate, which can result in anesthesia, sedation, and memory loss.

Educational objective:
Tetrahydrobiopterin (BH_4) is a cofactor used by hydroxylase enzymes in the synthesis of tyrosine, dopamine, and serotonin. Phenylketonuria can result from BH_4 deficiency due to dihydropteridine reductase deficiency. Intellectual disability is the hallmark of this condition and results in neurotransmitter (eg, serotonin) deficiency and hyperphenylalanemia. Treatment involves a low phenylalanine diet and BH_4 supplementation.

References

- Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies.

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- Disorders of Tetrahydrobiopterin Metabolism and their Treatment

Biochemistry	Nervous System	Phenylketonuria
Subject	System	Topic

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Biochemistry	Nervous System	Phenylketonuria
Subject	System	Topic

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A 46-year-old man comes to the emergency department due to recurrent nosebleeds. When interviewed for additional history, he becomes belligerent and uncooperative. The patient has a history of alcohol abuse and chronic mental illness. He has been placed in homeless shelters on multiple occasions but has not remained there for any prolonged periods. Physical examination shows swollen gums, scattered ecchymoses, and hyperkeratosis. He also has a chronic ulcer on the left lower extremity that does not appear to be infected. Which of the following mechanisms accounts for this patient's examination findings?

A. Abnormal oxidative decarboxylation of ketoacids

B. Abnormal proline hydroxylation

C. Abnormal transamination

D. Deficient methionine synthesis

E. Diminished synthesis of purines

Submit

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- A. Abnormal oxidative decarboxylation of ketoacids (4%)
- ✓ B. Abnormal proline hydroxylation (80%)
- C. Abnormal transamination (4%)
- D. Deficient methionine synthesis (5%)
- E. Diminished synthesis of purines (4%)

Omitted
Correct answer
B

80%
Answered correctly

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Explanation

Water-soluble vitamins		
Vitamin	Primary function	Deficiency

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Water-soluble vitamins

Vitamin	Primary function	Deficiency
B_1 (thiamine)	Decarboxylation of α-keto acids (carbohydrate metabolism)	• Beriberi (peripheral neuropathy, heart failure) • Wernicke-Korsakoff syndrome
B_2 (riboflavin)	Mitochondrial electron carrier (FMN, FAD)	• Angular cheilosis, stomatitis, glossitis • Normocytic anemia
B_3 (niacin)	Electron transfer reactions (NAD/NADP)	• Pellagra (dermatitis, dementia, diarrhea) • Peripheral neuropathy
B_6 (pyridoxine)	Transamination of amino acids (amino acid synthesis)	• Cheilosis, stomatitis, glossitis
B_9 (folate, folic acid)	Hydroxymethyl/formyl carrier (purine & thymine synthesis)	• Megaloblastic anemia • Neural tube defects (fetus)
	Isomerase &	

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B_9 (folate, folic acid)	Hydroxymethyl/formyl carrier (purine & thymine synthesis)	• Megaloblastic anemia • Neural tube defects (fetus)
B_{12} (cobalamin)	Isomerase & methyltransferase cofactor (DNA & methionine synthesis)	• Megaloblastic anemia • Neurologic deficits
C (ascorbic acid)	Hydroxylation of proline & lysine (collagen synthesis)	• Scurvy

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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug abusers). Symptoms of vitamin C deficiency are the result of decreased connective tissue strength. The capillary walls are especially fragile, leading to **easy bruising**, mucosal bleeding, and perifollicular petechial hemorrhages. Patients may also suffer from **periodontal disease** (gum swelling, loosening of the teeth, and infection) and **poor wound healing**, and have **hyperkeratotic follicles** with corkscrew hairs. Scurvy is even more severe in children and manifests with hemorrhages, bony deformities, and subperiosteal and joint hematomas.

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Vitamin C is necessary for the **hydroxylation of proline and lysine** residues during collagen synthesis. This reaction is executed by prolyl and lysyl hydroxylases, with vitamin C serving as a reducing agent. Hydroxyproline and hydroxylysine are essential for cross-linking collagen molecules. In scurvy, collagen cross-linking is compromised, thereby greatly reducing its tensile strength.

(Choice A) Thiamine (vitamin B_1) serves as a coenzyme in the decarboxylation reactions mediated by several dehydrogenase enzymes. It is necessary for the conversions of pyruvate to acetyl-CoA and of alpha-ketoglutarate to succinyl-CoA in the citric acid cycle. Vitamin B_1 deficiency can cause peripheral neuropathy, heart failure, and central nervous system dysfunction (Wernicke-Korsakoff syndrome).

(Choice C) Vitamin B_6 (pyridoxine) serves as a cofactor in many reactions that involve amino acids (eg, transamination, decarboxylation, deamination). Pyridoxine deficiency manifests with seborrheic dermatitis, glossitis, and peripheral neuropathy.

(Choice D) Vitamin B_{12} is necessary for the synthesis of methionine from homocysteine and for the synthesis of succinyl-CoA from methylmalonyl-CoA. Deficiency of vitamin B_{12} causes megaloblastic anemia and subacute combined degeneration of the spinal cord.

(Choice E) Purine and thymidine synthesis is diminished in patients with folate deficiency. The resultant decreased ability of erythropoietic cells to form DNA causes megaloblastic anemia.

Educational objective:
Vitamin C is necessary for the hydroxylation of proline and lysine residues in pro-collagen. Vitamin C deficiency (scurvy) is most often seen in severely malnourished individuals and leads to capillary bleeding, poor wound healing, and periodontal disease. In children, bony deformities and subperiosteal hemorrhages are also characteristic.

References

- Scurvy masquerading as leukocytoclastic vasculitis: a case report and review of the literature.

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References

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Biochemistry	Miscellaneous (Multisystem)	Vitamin C deficiency
Subject	System	Topic

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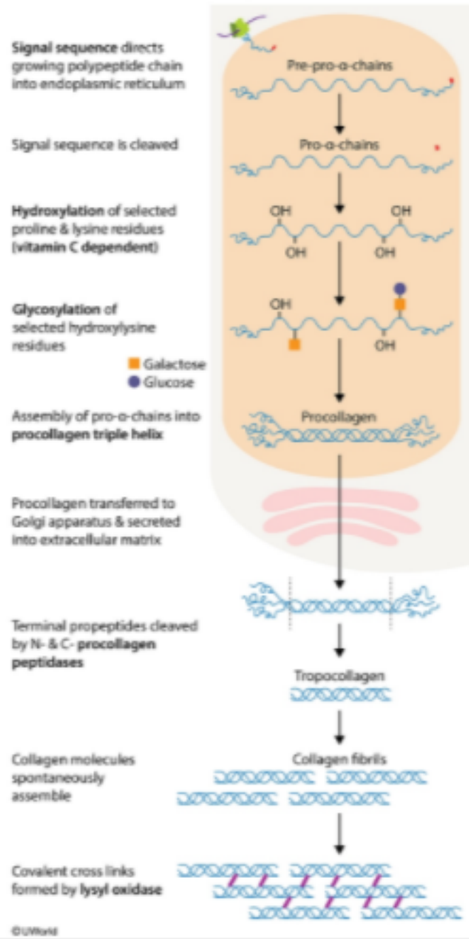
Exhibit Display

Collagen synthesis



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A 3-year-old boy is brought to the office due to abnormal motor development. He was born at 40 weeks gestation and had an unremarkable perinatal course. The boy developed normally during the first year of life. However, for the past 2 years, he has had progressive bilateral leg stiffness and abnormal involuntary movements. His cognitive and motor development is also delayed. There is no significant family history of neurological or muscular disorders. The patient's height, weight, and head circumference are below the 3rd percentile. Examination shows bilateral spastic paresis of his lower extremities and frequent choreoathetoid movements. Comprehensive laboratory testing reveals significantly elevated arginine levels in plasma and cerebrospinal fluid. The deficient enzyme in this patient is normally involved in the production of which of the following?

- A. γ-aminobutyric acid
- B. Glutamine
- C. Homocysteine
- D. Orotic acid
- E. Serotonin
- F. Urea

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A. γ-aminobutyric acid (18%)
B. Glutamine (9%)
C. Homocysteine (7%)
D. Orotic acid (11%)
E. Serotonin (2%)
✓ F. Urea (50%)

Omitted
Correct answer
F

50%
Answered correctly

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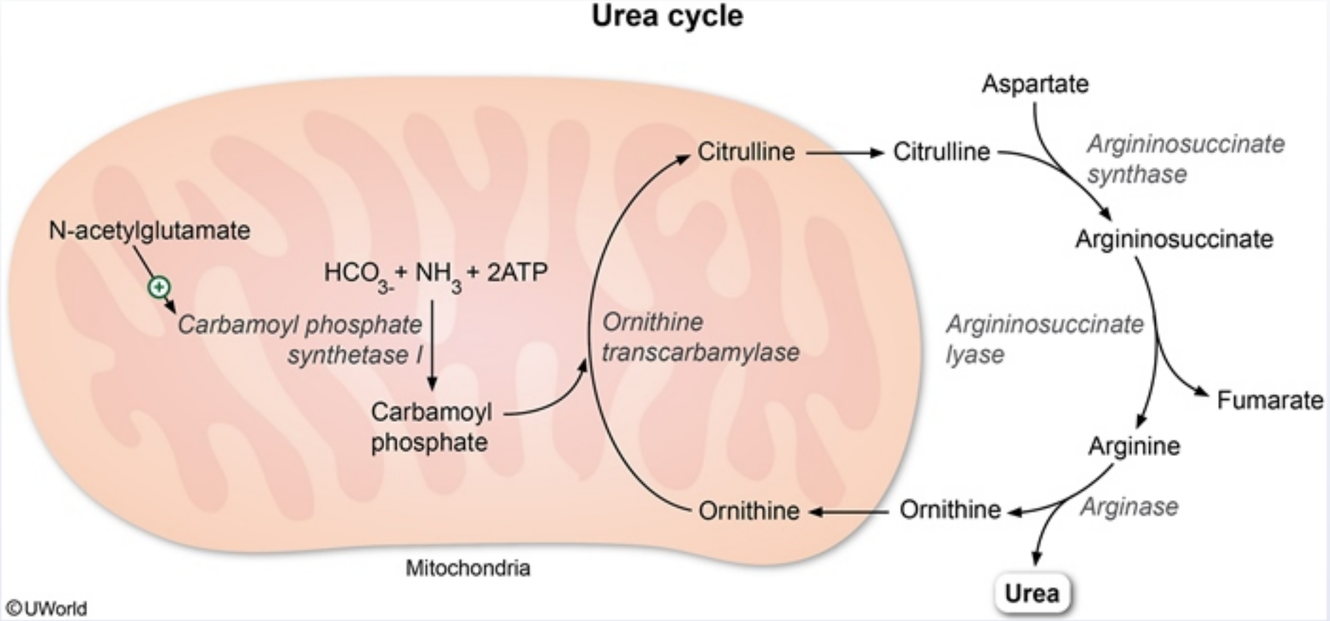
Explanation

Urea cycle

Explanation



This patient has features of **arginase deficiency**, including progressive development of **spastic diplegia**, **abnormal movements**, and growth delay in the setting of **elevated arginine levels**. Arginase is a urea cycle enzyme that produces **urea and ornithine** from arginine. Diagnosis is based on elevated arginine levels on plasma amino acid testing. Treatment of arginase deficiency consists of a **low-protein diet** devoid of arginine. Administration of a synthetic protein made of essential amino acids usually results in a dramatic decrease in plasma arginine concentration and an improvement in neurological abnormalities. Unlike other urea cycle disorders, patients with arginase deficiency have **mild or no hyperammonemia**.

(Choice A) The amino acid derivative γ-aminobutyrate (GABA) is a well-known inhibitor of presynaptic transmission in the retina and central nervous system. GABA is formed from glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase.

(Choice B) Glutamine is the major amino acid in the blood because it transports excess ammonia from peripheral tissues to the kidney. In the nephron, the amide nitrogen is hydrolyzed by glutaminase to regenerate glutamate and a free ammonium ion, which can then be excreted in the

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(Choice C) Deficiencies of vitamins B_6, B_{12}, and folate (B_9) are associated with hyperhomocysteinemia, which in turn is associated with atherosclerosis and thrombotic events.

(Choice D) Orotic acid is overproduced when a block in the urea cycle leads to excess carbamoyl phosphate, which is metabolized by dihydroorotate dehydrogenase to orotic acid. Excessive amounts of orotic acid are usually found in citrullinemia and ornithine transcarbamylase deficiency. These urea cycle disorders are also accompanied by hyperammonemia.

(Choice E) Serotonin (5-hydroxytryptamine) is formed by the hydroxylation and decarboxylation of tryptophan by tryptophan hydroxylase. In addition, serotonin is degraded by monoamine oxidase and also undergoes neuronal reuptake.

Educational objective:
Arginase is a urea cycle enzyme that produces urea and ornithine from arginine. Arginase deficiency results in progressive spastic diplegia, growth delay, and abnormal movements. Treatment includes an arginine-free, low-protein diet.

References

- Arginase-1 deficiency.
- Arginase Deficiency.

Biochemistry	Nervous System	Urea cycle
Subject	System	Topic

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A 34-year-old man develops severe chest and abdominal pain while shopping in a mall. Paramedics arrive and find him in severe distress. Several minutes later, he suffers a cardiac arrest with pulseless electrical activity and cannot be resuscitated. Postmortem examination reveals an internal hemorrhage as the cause of death. Histochemical evaluation of the patient's tissues reveals a defect affecting a large extracellular glycoprotein. This protein is normally found abundantly in large blood vessels, periosteum, and zonular fibers of the lens and functions to form microfibrils by surrounding elastin. This patient most likely suffered from which of the following conditions?

- A. Ehlers-Danlos syndrome
- B. Homocystinuria
- C. Marfan syndrome
- D. Osteogenesis imperfecta
- E. Polycystic kidney disease
- F. Vitamin C deficiency

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- A. Ehlers-Danlos syndrome (15%)
- B. Homocystinuria (1%)
- ✓ C. Marfan syndrome (80%)
- D. Osteogenesis imperfecta (1%)
- E. Polycystic kidney disease (0%)
- F. Vitamin C deficiency (0%)

Omitted
Correct answer
C

80%
Answered correctly

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01/23/2020
Last Updated

Explanation

Clinical features of Marfan syndrome	
	• Arachnodactyly

Clinical features of Marfan syndrome	
Skeletal	• Arachnodactyly • ↓ Upper-to-lower body segment ratio, ↑ arm-to-height ratio • Pectus deformity, scoliosis, or kyphosis • Joint hypermobility
Ocular	• Ectopia lentis
Cardiovascular	• Aortic dilation, regurgitation, or dissection • Mitral valve prolapse
Pulmonary	• Spontaneous pneumothorax from apical blebs
Skin	• Recurrent or incisional hernia • Skin striae

Fibrillin-1 is a major component of microfibrils that form a sheath around elastin fibers. Microfibrils are abundant in blood vessels (eg, aortic media), periosteum, and the suspensory ligaments of the lens. Fibrillin in the extracellular space acts as a scaffold for deposition of elastin extruded from connective tissue cells. Defects in fibrillin-1 cause mechanical weakening in the connective tissues and abnormal activation of transforming growth factor beta.

Marfan syndrome is caused by an inherited defect in the fibrillin-1 gene. Patients with Marfan syndrome can often be identified due to a characteristic body habitus, with long thin extremities, loose joints, and long fingers (arachnodactyly). The cause of death in Marfan syndrome is most often due to cardiovascular complications (eg, **aortic root dilation, dissection, and rupture**).

(Choice A) Ehlers-Danlos syndrome is a collection of heritable disorders of connective tissue characterized by skin and joint hypermobility. Like those with Marfan syndrome, these patients are at risk for aortic rupture. However, Ehlers-Danlos syndrome affects the formation and extracellular structuring of collagen rather than microfibrils.

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(Choice A) Ehlers-Danlos syndrome is a collection of heritable disorders of connective tissue characterized by skin and joint hypermobility. Like those with Marfan syndrome, these patients are at risk for aortic rupture. However, Ehlers-Danlos syndrome affects the formation and extracellular structuring of collagen rather than microfibrils.

(Choice B) Homocystinuria is a rare inherited metabolic disorder due to cystathionine synthase deficiency. It is characterized by very high circulating homocysteine levels, marfanoid habitus, and increased risk for premature atherosclerotic cardiovascular disease.

(Choice D) Osteogenesis imperfecta results from defects in the genes encoding type I collagen, a major component of bones. Defects in type I collagen in osteogenesis imperfecta result in reduced bone mass and fragility fractures. Other manifestations of the disease include blue sclera, dental abnormalities, and hearing loss.

(Choice E) Autosomal dominant polycystic kidney disease is a disorder of tubular epithelial cells. It causes enlargement of the kidneys with numerous parenchymal cysts. Patients are also at risk for cardiac valvular disorders and ruptured cerebral aneurysms.

(Choice F) Deficiency of vitamin C (scurvy) causes impaired hydroxylation of proline and lysine residues in collagen. Clinical features include skin fragility, easy bleeding, and poor dentition.

Educational objective:
Marfan syndrome is due to a defect in fibrillin-1, an extracellular glycoprotein that acts as a scaffold for elastin. It is abundant in the zonular fibers of the lens, periosteum, and aortic media. Aortic root dilation with dissection and rupture is a common cause of death.

References

- Molecular pathogenesis of Marfan syndrome.

Biochemistry	Rheumatology/Orthopedics & Sports	Marfan syndrome
Subject	System	Topic

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A 4-day-old girl is brought to the office for a routine newborn visit. She was born at 39 weeks gestation via normal spontaneous vaginal delivery to a gravida 5 para 4 woman. The patient has been breastfed exclusively but has had increasing difficulty feeding over the past 24 hours. Her parents say that she is "too sleepy to feed" and has been vomiting. The infant has 3 healthy, living siblings and a brother who died in infancy from "low sugar in his blood." Physical examination shows tachypnea and signs of dehydration. The patient is responsive to painful stimuli only. After acute treatment and stabilization, urine testing reveals significantly elevated levels of methylmalonic acid. Which of the following sets of laboratory values would most likely result from this patient's condition?

	Urine propionic acid	Serum glucose	Urine ketones	Serum ammonia
A.	Normal	↓	↑	Normal
B.	↑	↓	↑	↑
C.	Normal	↓	Negative	↑
D.	Normal	Normal	Negative	↑
E.	Normal	↓	↑	↓

Submit

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	Urine propionic acid	Serum glucose	Urine ketones	Serum ammonia
A. (15%)	Normal	↓	↑	Normal
✓ B. (47%)	↑	↓	↑	↑
C. (26%)	Normal	↓	Negative	↑
D. (3%)	Normal	Normal	Negative	↑
E. (7%)	Normal	↓	↑	↓

Omitted
Correct answer
B

47%
Answered correctly

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01/30/2020
Last Updated

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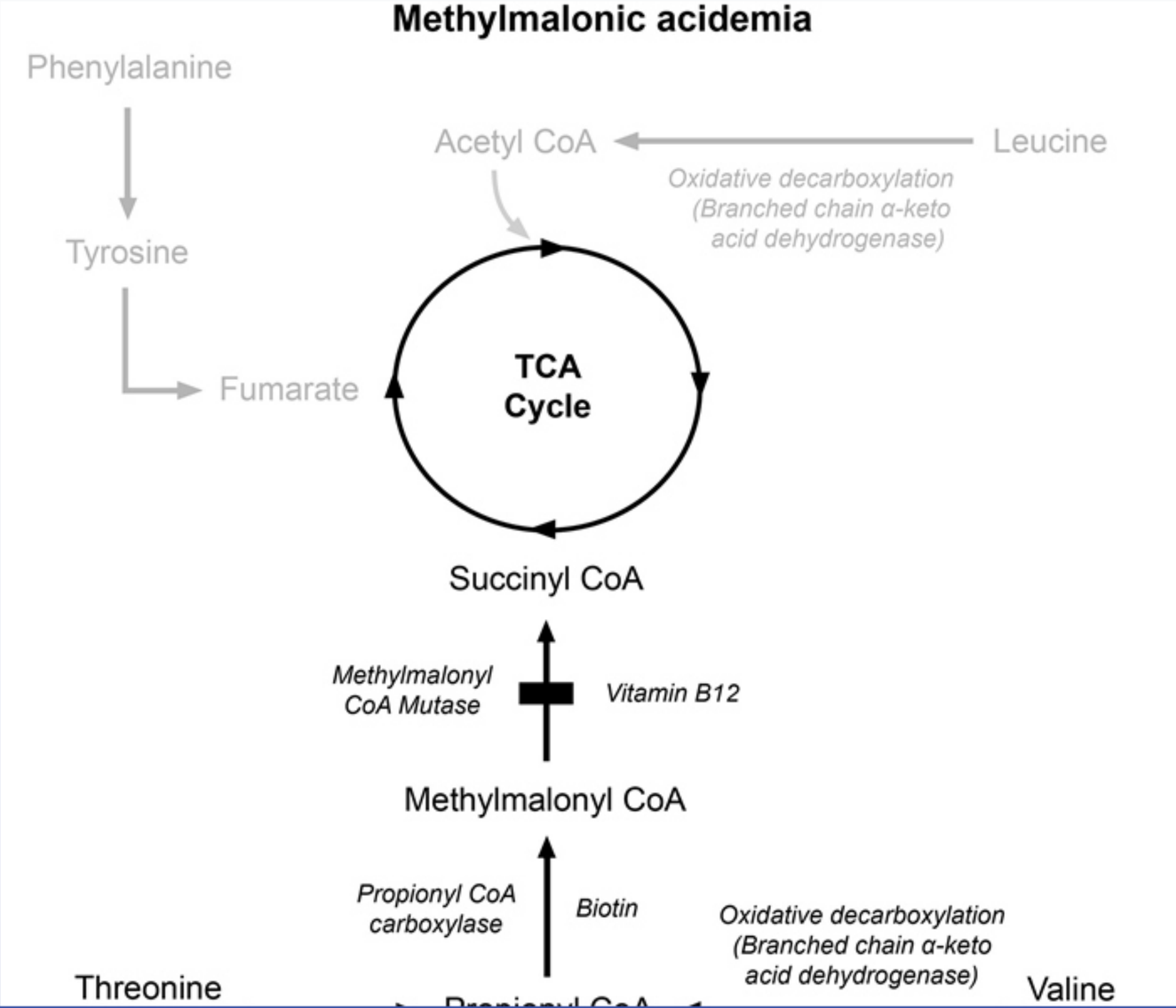

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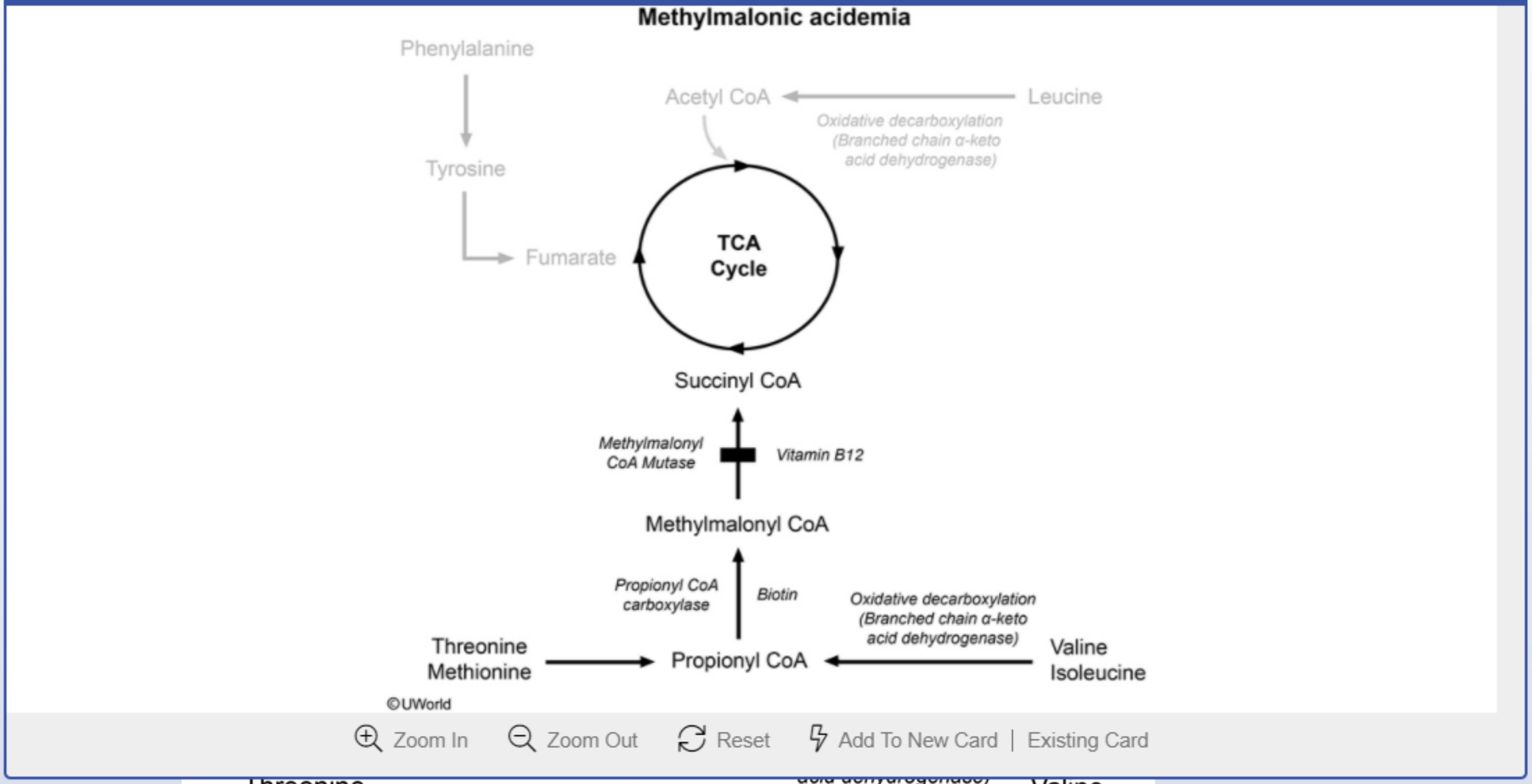

This patient's presentation is consistent with methylmalonic acidemia, an **autosomal recessive organic acidemia** resulting from complete or partial deficiency of the enzyme **methylmalonyl-CoA mutase**.

Catabolism of isoleucine, valine, threonine, methionine, and odd-chain fatty acids normally leads to formation of propionyl CoA, which is then converted to methylmalonyl CoA by biotin-dependent carboxylation. Isomerization of methylmalonyl CoA through a vitamin B12-dependent reaction forms succinyl CoA, which subsequently enters the TCA cycle. Mutations in methylmalonyl-CoA mutase result in buildup of methylmalonic acid and propionic acid, leading to a **metabolic acidosis**. **Hypoglycemia** results from overall increased metabolic rate leading to increased glucose utilization and direct toxic inhibition of gluconeogenesis by the organic acids. The presence of hypoglycemia leads to increased free fatty acid metabolism that produces **ketones**, resulting in a further anion gap metabolic acidosis. Finally, organic acids also directly inhibit the urea cycle, leading to **hyperammonemia**.

Complete deficiency of methylmalonyl-CoA mutase results in an anion gap metabolic acidosis, hypoglycemia, ketosis, and hyperammonemia. These metabolic derangements manifest as hypotonia, lethargy, vomiting, and respiratory distress (tachypnea due to acidosis) in the neonatal period. Diagnosis is confirmed by the presence of **elevated urine methylmalonic acid and propionic acid**.

Propionic acidemia, a deficiency in propionyl-CoA carboxylase, also results in hyperammonemia, hypoglycemia, and metabolic acidosis, although it does not display elevated levels of urine methylmalonic acid.

(Choice A) Production of ketones in the presence of hypoglycemia is an appropriate response in the fasting state, as ketones provide fuel for the brain. In this patient, the notable family history and elevated serum methylmalonic acid level make methylmalonic acidemia more likely than simple fasting or dehydration.

(Choice C) Fatty acid oxidation disorders, such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, can present with hypoglycemia, hyperammonemia, and metabolic acidosis, but these disorders lack an appropriate ketosis.

(Choice D) Urea cycle defects typically present with hyperammonemia without hypoglycemia or ketosis.

(Choice E) Propionic acid levels are elevated in patients with methylmalonic acidemia due to downstream enzymatic deficiency of methylmalonyl-CoA mutase.

Educational objective:

Methylmalonic acidemia is an organic acidemia due to complete or partial deficiency of methylmalonyl-CoA mutase. Complete deficiency

These metabolic derangements manifest as hypotonia, lethargy, vomiting, and respiratory distress (tachypnea due to acidosis) in the neonatal period. Diagnosis is confirmed by the presence of **elevated urine methylmalonic acid and propionic acid**.

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(Choice D) Urea cycle defects typically present with hyperammonemia without hypoglycemia or ketosis.

(Choice E) Propionic acid levels are elevated in patients with methylmalonic acidemia due to downstream enzymatic deficiency of methylmalonyl-CoA mutase.

Educational objective:
Methylmalonic acidemia is an organic acidemia due to complete or partial deficiency of methylmalonyl-CoA mutase. Complete deficiency classically presents with lethargy, vomiting, and tachypnea in a newborn. Laboratory testing shows hyperammonemia, ketotic hypoglycemia, and metabolic acidosis. The diagnosis is confirmed by elevated urine methylmalonic acid and propionic acid.

References

- Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia.

Biochemistry	Nervous System	Metabolic acidosis
Subject	System	Topic

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A 54-year-old woman is evaluated in the clinic for exertional dyspnea and easy fatigability. The patient has no chest pain, cough, or wheezing. She does not use tobacco, alcohol, or illicit drugs. On physical examination, her gait is unstable when her eyes are closed and there is impaired vibratory sensation in the lower extremities. Marked pallor of the conjunctivae, nail beds, and palms is present. Which of the following laboratory tests would help confirm the most likely diagnosis in this patient?

A. Erythrocyte glucose-6-phosphate dehydrogenase activity
B. Erythrocyte glutathione reductase activity
C. Erythrocytic pyruvate kinase activity
D. Erythrocyte transketolase activity
E. Serum methylmalonic acid level
F. Serum protoporphyrin level

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- A. Erythrocyte glucose-6-phosphate dehydrogenase activity (5%)
- B. Erythrocyte glutathione reductase activity (4%)
- C. Erythrocytic pyruvate kinase activity (3%)
- D. Erythrocyte transketolase activity (6%)
- ✓ E. Serum methylmalonic acid level (72%)
- F. Serum protoporphyrin level (7%)

Omitted
Correct answer
E

72%
Answered correctly

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01/28/2020
Last Updated

Explanation

Vitamin B_{12} deficiency

Impaired

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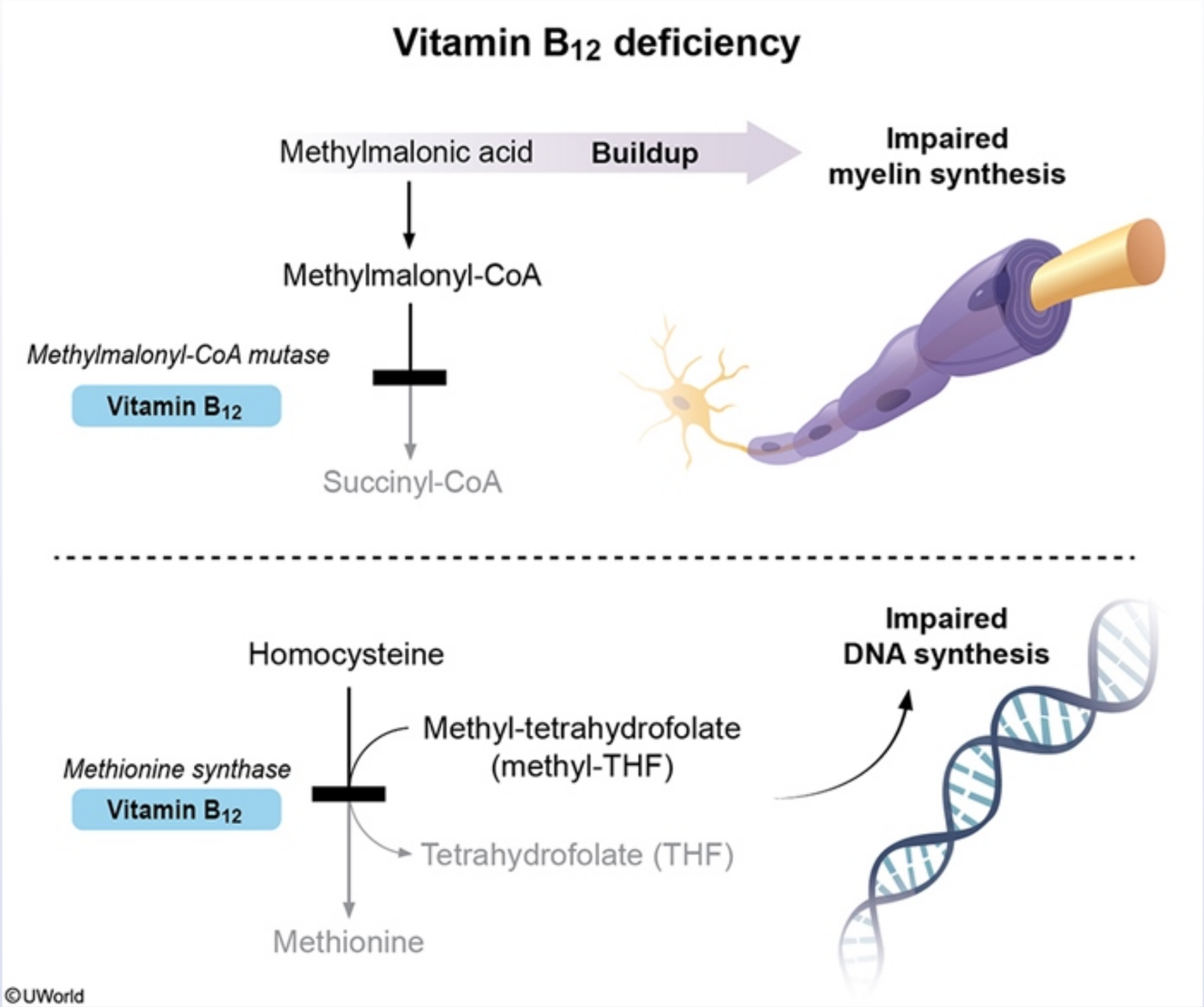

This patient has features of anemia (eg, exertional dyspnea, fatigue, pallor) with associated neurologic deficits that are highly suggestive of **vitamin B_{12} deficiency**. The hematologic manifestations of B_{12} deficiency (eg, **megaloblastic anemia**, pancytopenia) are related to impaired DNA synthesis.

Vitamin B_{12} (hydroxocobalamin) also serves as a cofactor for methylmalonyl-CoA mutase (converts methylmalonyl-CoA to succinyl-CoA) and methionine synthase (converts homocysteine and folic acid to methionine). B_{12} deficiency consequently results in **elevated** levels of **serum methylmalonic acid and homocysteine**. Increased methylmalonic acid levels can disrupt myelin synthesis and result in **subacute combined degeneration** of the dorsal columns (eg, loss of proprioception/vibration, Romberg sign) and lateral corticospinal tract (eg, spastic muscle weakness, hyperreflexia). Axonal degeneration of peripheral nerves can also be seen.

(Choice A) Glucose-6-phosphate dehydrogenase deficiency (G6PD) leads to acute hemolytic anemia in response to oxidative stress. Neurologic manifestations are not present in G6PD-associated anemia.

(Choice B) Erythrocyte glutathione reductase activity may be decreased in patients with vitamin B_2 (riboflavin) deficiency because glutathione reductase uses bound FAD (derived from vitamin B_2) and NADPH as cofactors to reduce disulfide bonds. Vitamin B_2 deficiency typically presents with normocytic anemia and inflammation of the lips (cheilosis), mouth (stomatitis), and/or tongue (glossitis).

(Choice C) Pyruvate kinase generates ATP through the conversion of phosphoenolpyruvate to pyruvate. Pyruvate kinase deficiency is an autosomal recessive condition that typically presents with congenital hemolytic anemia due to impaired glycolytic ATP generation.

(Choice D) Transketolase is an enzyme of the hexose monophosphate pathway that utilizes thiamine (vitamin B_1) as a coenzyme. Erythrocyte transketolase activity is decreased in thiamine deficiency, which causes Wernicke-Korsakoff syndrome and beriberi.

(Choice F) Serum protoporphyrin levels are increased in iron deficiency anemia, lead poisoning, and erythropoietic protoporphyria. Lead poisoning can cause sideroblastic anemia and peripheral neuropathy, but other characteristic features (eg, abdominal/musculoskeletal pain, cognitive impairment, nephropathy) are not evident in this patient.

Educational objective:
Vitamin B_{12} deficiency often presents with megaloblastic anemia (impaired DNA synthesis) and neurologic deficits (impaired myelin synthesis). Characteristic neurologic findings include subacute combined degeneration of the dorsal columns and lateral corticospinal tract. Elevations in methylmalonic acid and homocysteine levels occur due to decreased metabolism of these molecules.

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References

- Clinical practice. Vitamin B12 deficiency.

Biochemistry	Nervous System	Vitamin b12 deficiency
Subject	System	Topic

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A 4-month-old boy is being evaluated for a hereditary metabolic disorder after presenting with failure to thrive and developmental delay. He was born outside the United States and had several seizures during the neonatal period. Physical examination reveals an abnormal head shape with a large anterior fontanelle and widely splayed cranial sutures. Profound hypotonia and hepatomegaly are also noted. Biochemical studies show elevated levels of very long chain fatty acids (VLCFAs) and phytanic acid. Cultured skin fibroblasts show impaired ability to oxidize VLCFAs. This patient's condition is best explained by dysfunction of which of the following cellular structures?

- A. Golgi apparatus
- B. Lysosomes
- C. Mitochondria
- D. Peroxisomes
- E. Proteasomes
- F. Rough endoplasmic reticulum

Submit

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- A. Golgi apparatus (2%)
- B. Lysosomes (12%)
- C. Mitochondria (22%)
- ✓ D. Peroxisomes (56%)
- E. Proteasomes (3%)
- F. Rough endoplasmic reticulum (1%)

Omitted
Correct answer
D

56%
Answered correctly

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Last Updated

Explanation

Functions of cellular organelles	
Golgi apparatus	• Protein modification, sorting & transport

Functions of cellular organelles	
Golgi apparatus	• Protein modification, sorting & transport
Lysosomes	• Digestion of cellular debris & pathogens
Mitochondria	• TCA cycle & fatty acid oxidation • Electron transport chain (ATP synthesis) • Apoptosis
Peroxisomes	• Oxidation of very long & branched-chain fatty acids • Hydrogen peroxide degradation
Proteasomes	• Degradation of ubiquitinated proteins
Rough endoplasmic reticulum	• Synthesis of integral membrane & secretory proteins
Smooth endoplasmic reticulum	• Drug detoxification • Lipid, phospholipid & steroid synthesis

Peroxisomal disorders are rare inborn errors of metabolism in which **peroxisomes** are either absent or nonfunctional. **Very long chain fatty acids** (VLCFAs) and certain **branched-chain fatty acids** (eg, phytanic acid) cannot undergo mitochondrial beta-oxidation; these fatty acids are metabolized by a special form of beta-oxidation (VLCFAs) or by alpha-oxidation (branched-chain fatty acids) within peroxisomes. In peroxisomal disorders, these fatty acids build up in various tissues. Accumulation in neuronal cell membranes leads to **neurologic defects** due to improper neuronal migration, myelination, and degeneration.

This infant most likely has **Zellweger syndrome**, which is caused by defective peroxisomal biogenesis. It typically presents in early infancy with craniofacial abnormalities (eg, widened sutures, large anterior fontanelle), hepatomegaly, and profound neurologic defects (eg, hypotonia, seizures, developmental delay). Death usually occurs within months of initial presentation.

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Another common peroxisomal disease is **X-linked adrenoleukodystrophy**, which is characterized by defective transport of VLCFAs into peroxisomes. Patients present in childhood or adulthood with neurologic deterioration and adrenal insufficiency as VLCFAs accumulate in the central nervous system and adrenal glands.

(Choice A) The Golgi apparatus is involved in posttranslational modification of proteins from the rough endoplasmic reticulum. It also routes proteins to their ultimate location (eg, lysosomes, extracellular space) using membrane-bound vesicles.

(Choice B) Lysosomes are organelles containing proteins that can digest a diverse range of biomolecules, cellular debris, and engulfed pathogens. Lysosomal storage disorders (eg, mucopolysaccharidoses, sphingolipidoses) result in intracellular accumulation of glycosaminoglycans, glycoproteins, or glycolipids.

(Choice C) Mitochondria are responsible for beta-oxidation of most fatty acids, ketogenesis, the TCA cycle and electron transport chain, and the first 2 steps of the urea cycle. Dysfunction can lead to various types of encephalomyopathy. Mitochondria do not metabolize VLCFAs or fatty acids with branch points at odd-numbered carbons.

(Choice E) Proteasomes degrade unneeded or defective intracellular proteins into small polypeptides or amino acids. Impaired proteasome function can lead to cell cycle dysregulation, protein aggregation, and defective processing of peptide antigens.

(Choice F) The rough endoplasmic reticulum is the site of synthesis for most secretory proteins, integral membrane proteins of the nucleus and cell membrane, and lysosomal proteins.

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(Choice F) The rough endoplasmic reticulum is the site of synthesis for most secretory proteins, integral membrane proteins of the nucleus and cell membrane, and lysosomal proteins.

Educational objective:
The buildup of very long chain and branched-chain (eg, phytanic) fatty acids due to impaired oxidation is the hallmark of peroxisomal disorders (eg, Zellweger syndrome, adrenoleukodystrophy). Accumulation of these fatty acids in the brain results in permanent neurologic dysfunction.

References

- Peroxisome biogenesis disorders in the Zellweger spectrum: An overview of current diagnosis, clinical manifestations, and treatment guidelines.
- Zellweger spectrum disorders: clinical overview and management approach.

Biochemistry Nervous System Peroxisomal disorders

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A 61-year-old man is brought to the emergency department after being found unresponsive on a sidewalk. Paramedics notice that the patient's breath smells of alcohol and that he has vomitus in his mouth. The patient also has agonal respirations, and cardiac monitoring shows pulseless electrical activity. Resuscitation efforts are unsuccessful, and he is pronounced dead on arrival. Autopsy reveals that the cause of death is airway occlusion by aspirated vomitus. In addition, foci of hemorrhage and necrosis are seen in the mammillary bodies and gray matter surrounding the third and fourth ventricles. This patient's brain findings are most likely associated with a decrease in which of the following?

A. Blood protoporphyrin level

B. Erythrocyte glucose-6-phosphate dehydrogenase activity

C. Erythrocyte glutathione reductase activity

D. Erythrocyte transketolase activity

E. Serum methylmalonic acid level

F. Serum NADPH level

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A. Blood protoporphyrin level (2%)
B. Erythrocyte glucose-6-phosphate dehydrogenase activity (7%)
C. Erythrocyte glutathione reductase activity (12%)
✓ D. Erythrocyte transketolase activity (48%)
E. Serum methylmalonic acid level (11%)
F. Serum NADPH level (17%)

Omitted
Correct answer
D

48%
Answered correctly

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Last Updated

Explanation

Wernicke encephalopathy classically presents with the triad of ophthalmoplegia, ataxia, and confusion, and can lead to coma and death if left untreated. Foci of **hemorrhage and necrosis** in the **mammillary bodies** and periaqueductal gray matter are typically found on autopsy. This condition occurs due to chronic thiamine deficiency, which is common in patients with **alcoholism**.

Wernicke encephalopathy classically presents with the triad of ophthalmoplegia, ataxia, and confusion, and can lead to coma and death if left untreated. Foci of **hemorrhage and necrosis** in the **mammillary bodies** and periaqueductal gray matter are typically found on autopsy. This condition occurs due to chronic thiamine deficiency, which is common in patients with **alcoholism**.

Thiamine (vitamin B_1) participates in glucose metabolism and is a cofactor for the following enzymes:

1. Pyruvate dehydrogenase, which converts pyruvate (glycolysis end product) into acetyl-CoA (enters the citric acid cycle)
2. α-Ketoglutarate dehydrogenase, an enzyme of the citric acid cycle
3. Branched-chain α-ketoacid dehydrogenase, which is essential for catabolism of branched-chain amino acids (eg, leucine, isoleucine, valine)
4. Transketolase, an enzyme of the pentose phosphate pathway that helps convert ribulose 5-P (derived from glucose) to glycolysis intermediates (eg, glyceraldehyde 3-P)

Thiamine deficiency, therefore, results in decreased glucose utilization, which is especially pronounced in the central nervous system. If a patient with chronic thiamine deficiency is given a glucose infusion without thiamine supplementation, acute cerebral damage may occur. Thiamine deficiency can be diagnosed if baseline **erythrocyte transketolase activity** is low but increases after addition of thiamine pyrophosphate. In actual practice, if a patient is suspected of alcoholism or malnutrition, thiamine deficiency should be presumed and he or she should receive thiamine supplementation with glucose infusion.

(Choice A) Protoporphyrin is a precursor of heme. Increased erythrocyte protoporphyrin concentration is the hallmark of erythropoietic protoporphyria; however, this elevation is nonspecific and can be seen in other conditions (eg, iron deficiency anemia, lead poisoning).

(Choice B) Erythrocyte glucose-6-phosphate dehydrogenase (G6PD) catalyzes the rate-limiting step in the pentose phosphate pathway, which is necessary for production of NADPH and proper functioning of the erythrocyte antioxidant system. Decreased G6PD levels cause hemolytic anemia.

(Choices C and F) NADH and NADPH are both derived from niacin (vitamin B_3). NADPH is a cofactor for glutathione reductase, an enzyme that helps metabolize harmful reactive oxygen species. Neither NADPH nor erythrocyte glutathione reductase is used for diagnosing thiamine deficiency.

(Choice E) Methylmalonic acid, a product of fatty acid oxidation, is converted to succinyl-CoA by the enzyme methylmalonyl-CoA mutase (uses

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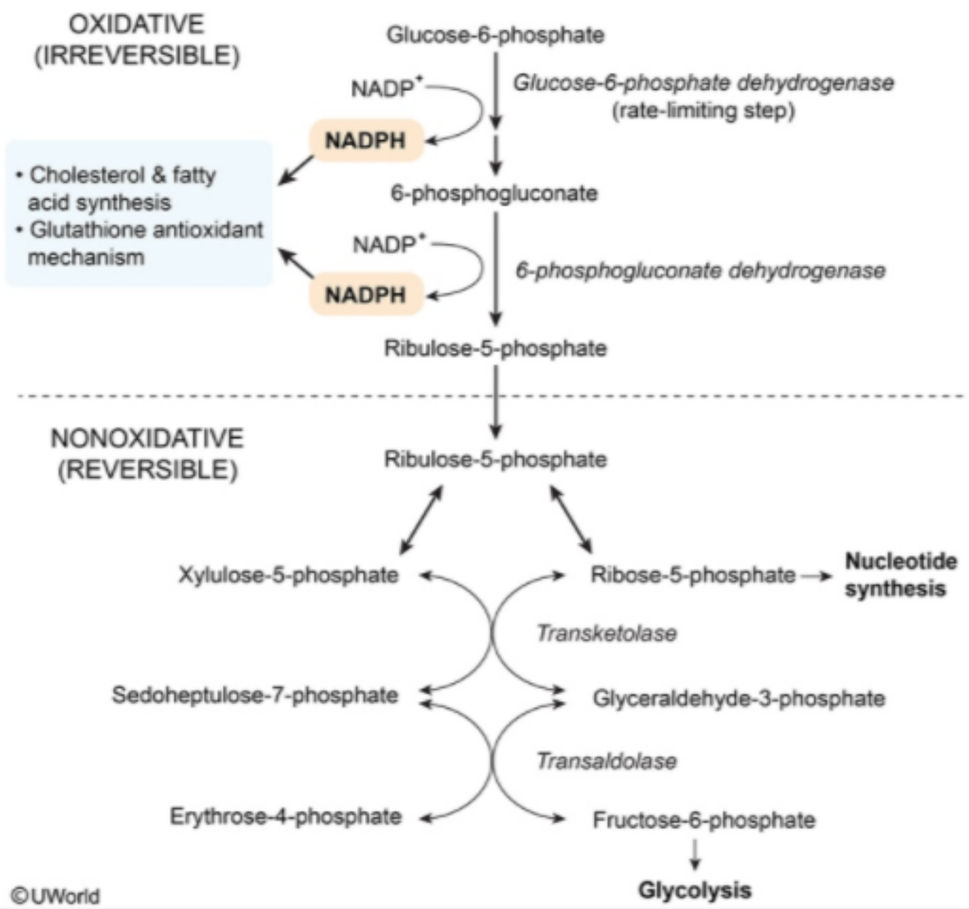

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(Choice E) Methylmalonic acid, a product of fatty acid oxidation, is converted to succinyl CoA by the enzyme methylmalonyl CoA mutase (uses

Thiamine deficiency can be diagnosed if baseline **erythrocyte transketolase activity** is low but increases after addition of thiamine pyrophosphate. In actual practice, if a patient is suspected of alcoholism or malnutrition, thiamine deficiency should be presumed and he or she should receive thiamine supplementation with glucose infusion.

(Choice A) Protoporphyrin is a precursor of heme. Increased erythrocyte protoporphyrin concentration is the hallmark of erythropoietic protoporphyria; however, this elevation is nonspecific and can be seen in other conditions (eg, iron deficiency anemia, lead poisoning).

(Choice B) Erythrocyte glucose-6-phosphate dehydrogenase (G6PD) catalyzes the rate-limiting step in the pentose phosphate pathway, which is necessary for production of NADPH and proper functioning of the erythrocyte antioxidant system. Decreased G6PD levels cause hemolytic anemia.

(Choices C and F) NADH and NADPH are both derived from niacin (vitamin B_3). NADPH is a cofactor for glutathione reductase, an enzyme that helps metabolize harmful reactive oxygen species. Neither NADPH nor erythrocyte glutathione reductase is used for diagnosing thiamine deficiency.

(Choice E) Methylmalonic acid, a product of fatty acid oxidation, is converted to succinyl-CoA by the enzyme methylmalonyl-CoA mutase (uses vitamin B_{12} as a cofactor). Consequently, methylmalonic acid levels are increased in vitamin B_{12} deficiency.

Educational objective:
Chronic thiamine (vitamin B_1) deficiency impairs glucose utilization in the central nervous system. This occurs due to decreased activity of the enzymes that use thiamine as a cofactor (eg, pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, transketolase). Thiamine deficiency can be diagnosed if baseline erythrocyte transketolase activity is low but increases after addition of thiamine pyrophosphate.

References

- Thiamine deficiency and delirium.

Biochemistry	Nervous System	Wernicke korsakoff syndrome
Subject	System	Topic

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A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

- A. Ascorbic acid
- B. Carnitine
- C. Pyridoxine
- D. Thiamine
- E. Tyrosine
- F. Vitamin K

Submit

A 5-year-old boy with developmental delay is brought to the office due to difficulty "seeing the board" at school. Examination shows a boy with a tall, thin habitus with elongated limbs. Funduscopy shows bilateral lens subluxation. Four years later, the patient dies suddenly of a massive cerebrovascular accident. Autopsy shows middle cerebral artery thrombosis and old renal infarcts. His parents wish to know if anything could have been done to have prevented his death. Which of the following would have been the most appropriate supplementation for this patient?

- A. Ascorbic acid (31%)
- B. Carnitine (7%)
- ✓ C. Pyridoxine (39%)
- D. Thiamine (5%)
- E. Tyrosine (6%)
- F. Vitamin K (9%)

Omitted
Correct answer
C

39%
Answered correctly

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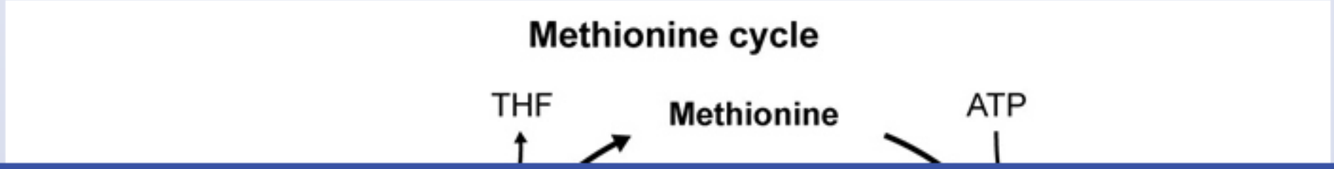
Time Spent

03/11/2020
Last Updated

Explanation



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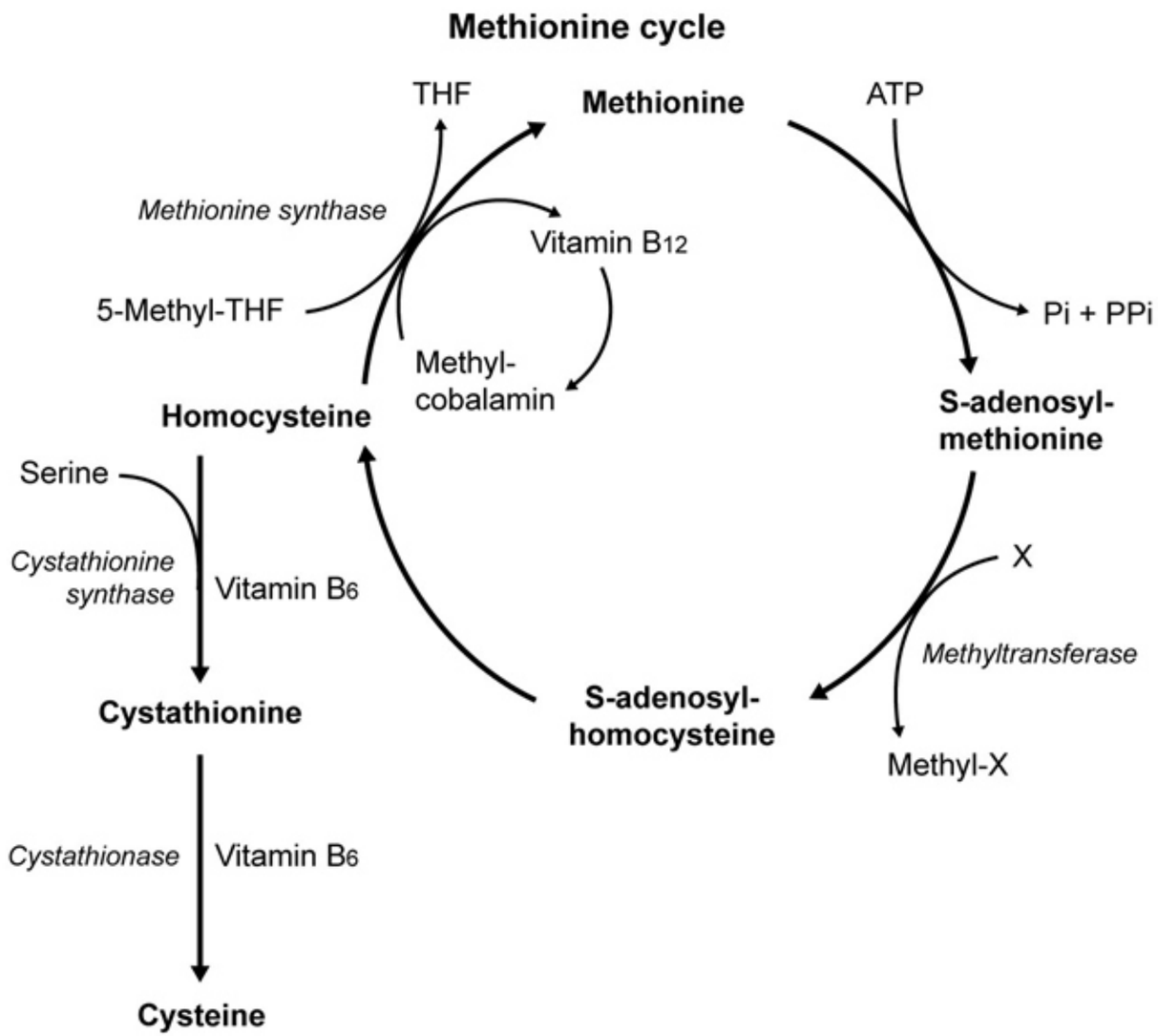

ATP = adenosine 5'-triphosphate; Pi = inorganic orthophosphate;

This patient's presentation is most consistent with homocystinuria, the most common inborn error of methionine metabolism. Most patients present at age 3-10 with **ectopia lentis (dislocated lens)**. About half of patients have **intellectual disability**. Other clinical manifestations include a Marfanoid habitus (eg, elongated limbs, arachnodactyly, scoliosis). Patients are at high risk for **thromboembolic occlusion** of both large and small vessels, especially those of the brain, heart, and kidneys. Thromboembolic complications are the major cause of morbidity and mortality in these patients.

Homocystinuria is most frequently caused by an **autosomal recessive** deficiency of cystathionine beta-synthase, an enzyme that requires **pyridoxine (vitamin B6)** as a cofactor. Approximately 50% of affected patients respond to high doses of pyridoxine, which improves residual enzymatic activity and reduces plasma homocysteine levels. Additional treatment includes dietary **restriction of methionine**.

(Choice A) Vitamin C is a necessary cofactor for the hydroxylation of proline and lysine residues in collagen. Vitamin C deficiency results in decreased strength of collagen fibers and causes scurvy.

(Choice B) Carnitine assists with long-chain fatty acid transport into mitochondria. Deficiencies in carnitine (eg, primary systemic carnitine deficiency) lead to fatty acid oxidation defects in cardiac and skeletal muscle.

(Choice D) Thiamine (vitamin B1) deficiency can cause dry and wet beriberi and Wernicke-Korsakoff syndrome.

(Choice E) Tyrosine is a nonessential amino acid and the precursor for catecholamines such as dopamine, epinephrine, and norepinephrine.

(Choice F) Vitamin K is involved in the post-translational conversion of glutamate to gamma-carboxyglutamic acid. This modification is necessary for the function of many clotting factors and regulatory proteins involved in the coagulation cascade.

Educational objective:
Homocystinuria is most commonly caused by cystathionine synthase deficiency. Affected individuals have marfanoid habitus, ectopia lentis, and developmental delay. Significant morbidity and mortality are due primarily to thromboembolism. Many patients with homocystinuria respond dramatically to pyridoxine (vitamin B6) supplementation.

References

- Hypermethioninemias of genetic and non-genetic origin: A review.
- Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects.

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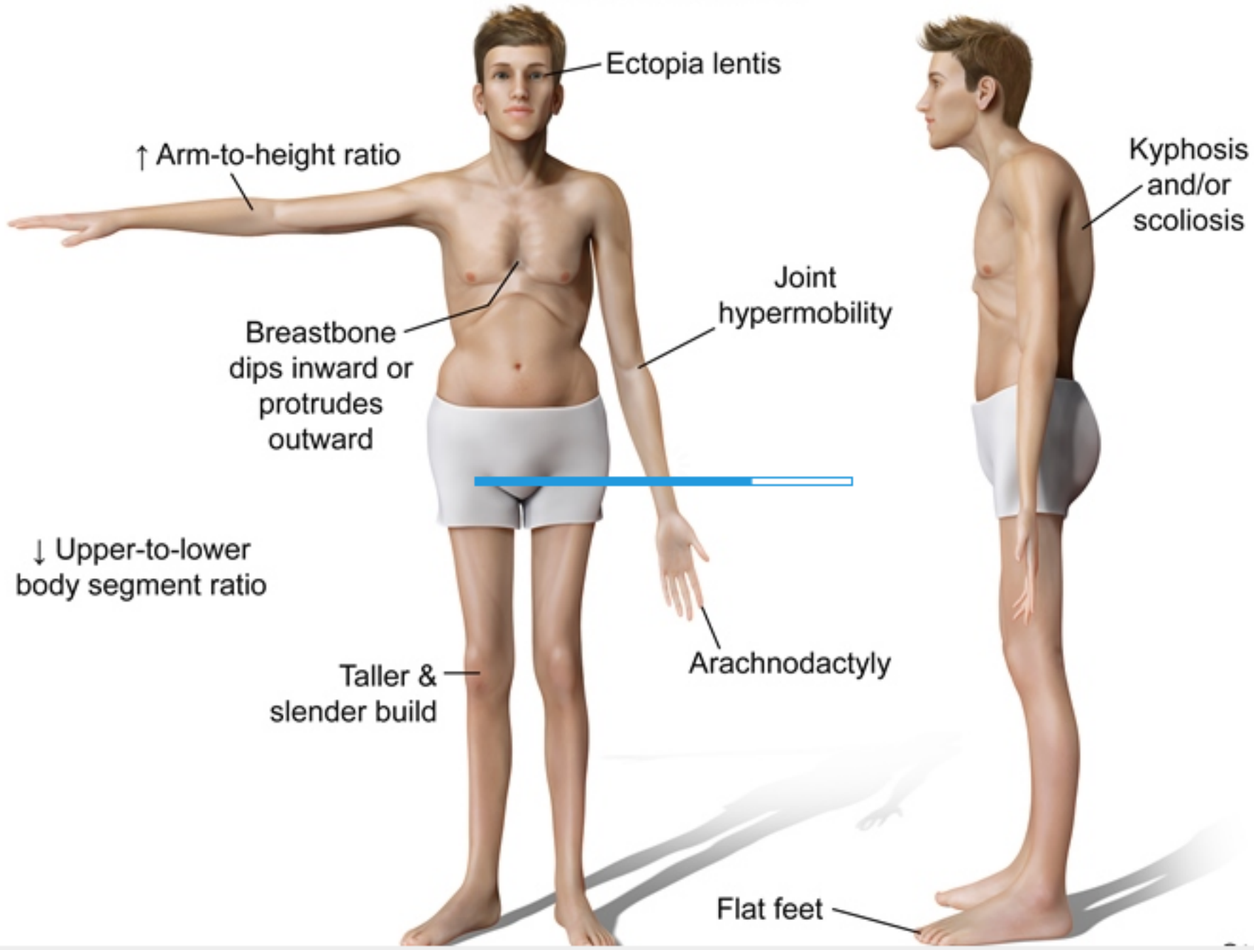

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- Overview of homocysteine and folate metabolism. With special references to cardiovascular disease and neural tube defects.

Biochemistry	Miscellaneous (Multisystem)	Homocystinuria
Subject	System	Topic

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

As part of a long-term cohort study, members of a large extended family undergo periodic analysis of multiple serum markers. Many male participants are found to have abnormal laboratory results despite no obvious signs of disease. Further analysis shows that these men have an X-linked mutation affecting the phosphoribosyl pyrophosphate (PRPP) synthetase gene, resulting in greatly increased substrate conversion.

Item 1 of 2

Which of the following organs is most likely to develop pathology secondary to this mutation?

- A. Aorta
- B. Heart
- C. Joints
- D. Liver
- E. Pancreas

Submit

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Item 1 of 2

Which of the following organs is most likely to develop pathology secondary to this mutation?

A. Aorta (2%)
B. Heart (5%)
✓ C. Joints (55%)
D. Liver (33%)
E. Pancreas (4%)

Omitted
Correct answer
C

55%
Answered correctly

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06/21/2020
Last Updated

Explanation

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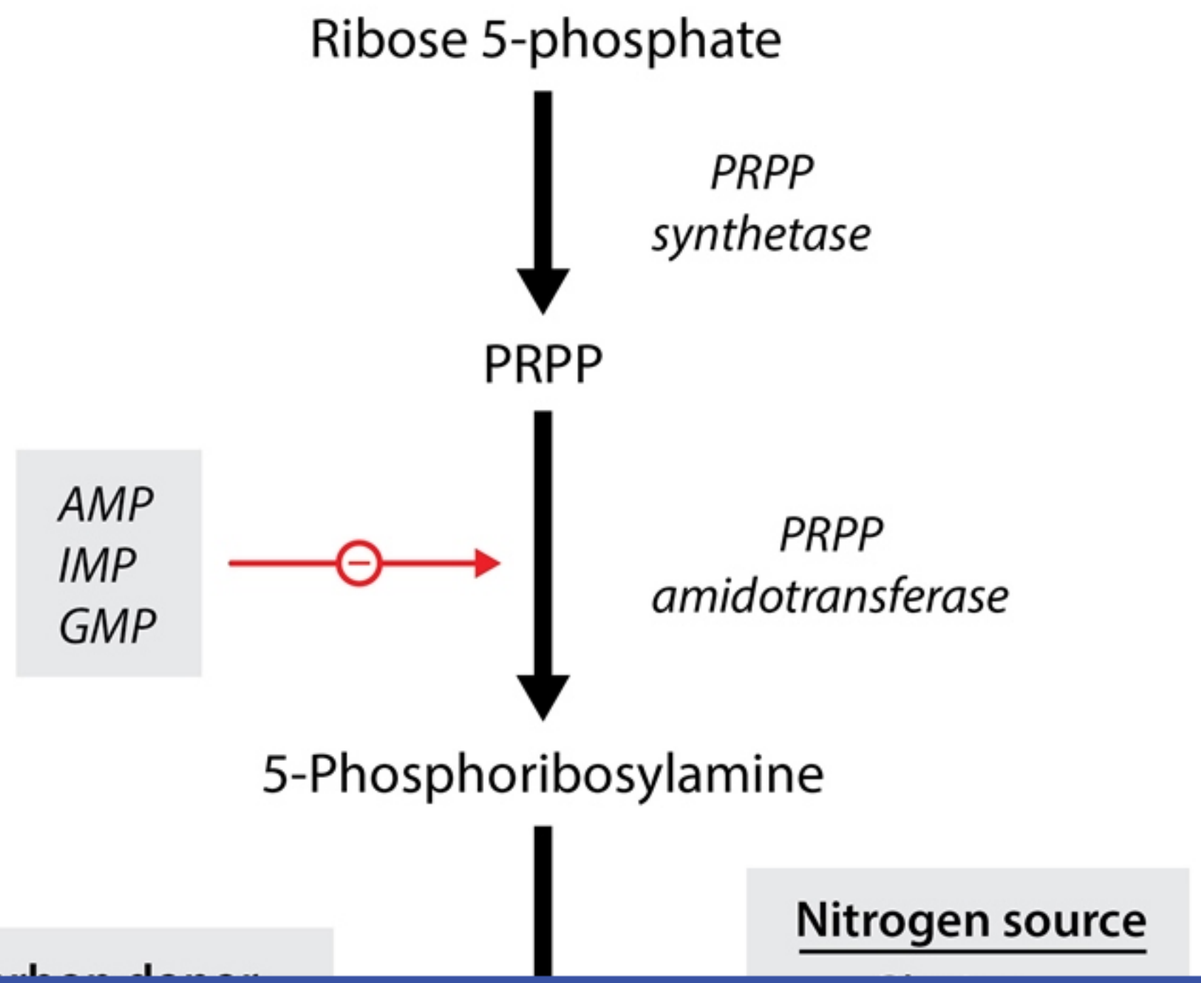
De novo purine synthesis



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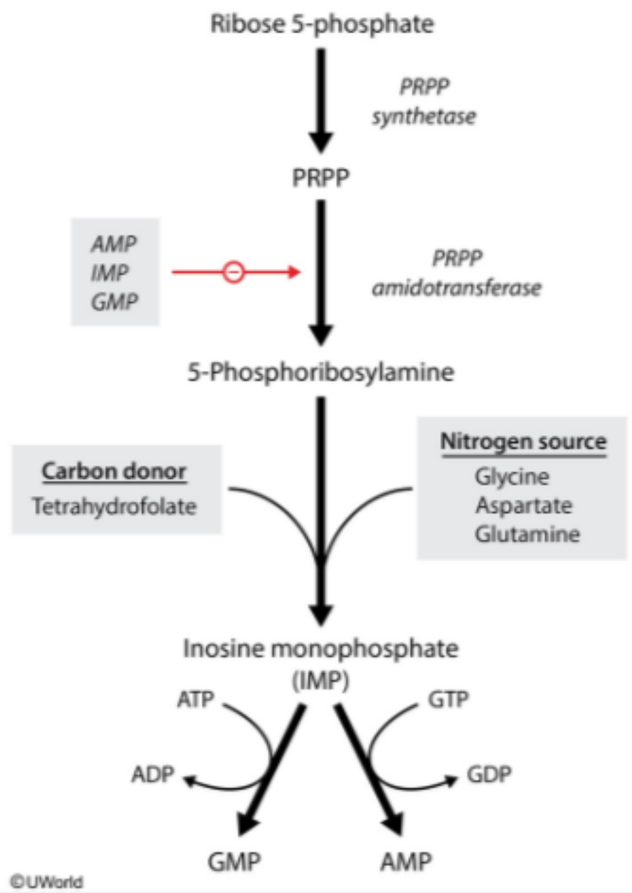

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Gout is a disease caused by tissue deposition of monosodium urate crystals. Elevated uric acid levels are a known risk factor for gout and increased purine metabolism is one possible cause of hyperuricemia. Phosphoribosyl pyrophosphate (PRPP) synthetase is the enzyme responsible for the production of the activated ribose necessary for de novo synthesis of purine and pyrimidine nucleotides. The mutation described in the question stem will cause increased production of purines due to feed-forward activation of the purine synthesis pathway. As a result, more purine molecules will undergo degradation, resulting in hyperuricemia and an increased risk of gout.

(Choice A) The aorta can develop aneurysms in patients with Marfan syndrome, which results from defects in fibrillin-1.

(Choices B and D) The heart and liver can be affected by glycogen storage diseases resulting from a variety of enzyme deficiencies such as glucose-6-phosphatase deficiency (von Gierke disease) and acid maltase deficiency (Pompe disease).

(Choice E) The pancreas is affected in patients with cystic fibrosis, which results from a mutation in the cystic fibrosis transmembrane conductance regulator gene. Common sequelae include pancreatitis, pancreatic insufficiency, and destruction of islet cells.

Educational objective:
Gout occurs with increased frequency in patients with activating mutations involving phosphoribosyl pyrophosphate synthetase due to increased production and degradation of purines.

References

- Inherited superactivity of phosphoribosylpyrophosphate synthetase: association of uric acid overproduction and sensorineural deafness.

Biochemistry	Rheumatology/Orthopedics & Sports	Gout
Subject	System	Topic

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Item 2 of 2

Incidentally, one of the male patients followed in the study is hospitalized with right knee pain and swelling. A sample of his synovial fluid shows negatively birefringent crystals under polarized light microscopy. To achieve rapid improvement in this patient's symptoms, therapy should be directed toward inhibiting which of the following types of cells?

- A. Eosinophils
- B. Lymphocytes
- C. Neutrophils
- D. Synovial cells
- E. Mast cells

Submit

Item 2 of 2

Incidentally, one of the male patients followed in the study is hospitalized with right knee pain and swelling. A sample of his synovial fluid shows negatively birefringent crystals under polarized light microscopy. To achieve rapid improvement in this patient's symptoms, therapy should be directed toward inhibiting which of the following types of cells?

- A. Eosinophils (2%)
- B. Lymphocytes (14%)
- ✓ C. Neutrophils (70%)
- D. Synovial cells (6%)
- E. Mast cells (5%)

Omitted
Correct answer
C

70%
Answered correctly

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Time Spent

06/21/2020
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Explanation

Acute gouty arthritis	
Signs &	• Usually involves **first metatarsophalangeal joint** or knee

Acute gouty arthritis	
Signs & symptoms	• Usually involves **first metatarsophalangeal joint** or knee • Swelling, erythema & **exquisite tenderness** • Symptoms develop rapidly over 24 hours
Diagnosis	• Joint aspiration shows **needle-shaped, negatively birefringent crystals**
Treatment	• Nonsteroidal anti-inflammatory drugs (eg, naproxen, indomethacin) preferred if no contraindications • Colchicine used as second-line therapy

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This patient's synovial fluid analysis shows negatively birefringent crystals (ie, monosodium urate crystals) under polarized light, which is diagnostic for gouty arthritis. Neutrophils are the primary cells responsible for the intense inflammatory response seen in patients with gout. Phagocytosis of urate crystals by neutrophils causes the release of various cytokines and inflammatory mediators that lead to further neutrophil activation and chemotaxis, resulting in a positive feedback loop that amplifies the inflammatory response.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for treating acute gouty arthritis. They inhibit prostanoid biosynthesis (eg, prostaglandins, prostacyclin, thromboxanes), exerting a broad anti-inflammatory effect that includes inhibition of neutrophils. Patients with contraindications to NSAIDs (eg, peptic ulcer disease, renal impairment) are often treated with colchicine, which impairs neutrophil migration and phagocytosis by interfering with microtubule formation. Colchicine also decreases tyrosine phosphorylation in response to monosodium urate crystals, resulting in decreased neutrophil activation.

(Choice A) Eosinophils function in defense against parasitic infections and are also pathogenic in patients with asthma, allergy, hypereosinophilic

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(Choice A) Eosinophils function in defense against parasitic infections and are also pathogenic in patients with asthma, allergy, hypereosinophilic syndromes, and vasculitides such as Churg-Strauss syndrome.

(Choice B) Lymphocytes produce delayed-type hypersensitivity reactions that do not play a role in gout.

(Choice D) Synovial cells and macrophages play a role in initiating the inflammatory response in gouty arthritis. However, targeting these cells would not eliminate the inflammatory amplification caused by neutrophils, which is the central mechanism involved in precipitating an acute gouty attack.

(Choice E) Mast cell degranulation can be inhibited by medications such as cromolyn sodium, which is used in conditions such as asthma and allergic rhinitis.

Educational objective:
Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for treating acute gouty arthritis. They inhibit cyclooxygenase and exert a broad anti-inflammatory effect that includes inhibition of neutrophils. When NSAIDs are contraindicated (eg, peptic ulcer disease, renal impairment), colchicine is useful in the acute management of gout as it inhibits neutrophil chemotaxis and phagocytosis by preventing microtubule formation.

References

(Choice A) Eosinophils function in defense against parasitic infections and are also pathogenic in patients with asthma, allergy, hypereosinophilic syndromes, and vasculitides such as Churg-Strauss syndrome.

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References

- Crystal-induced neutrophil activation. III. Inflammatory microcrystals induce a distinct pattern of tyrosine phosphorylation in human neutrophils.
- Prevention of neutrophil apoptosis by monosodium urate crystals.
- Colchicine: its mechanism of action and efficacy in crystal-induced inflammation.

Biochemistry	Rheumatology/Orthopedics & Sports	Gout
Subject	System	Topic

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A 34-year-old woman with a history of recurrent urinary tract infections comes to the physician with dysuria and increased urinary frequency. Her urine culture grows colonies of Gram-negative bacteria. The bacteria are isolated and placed in a growth-enhancing nutrient solution, where they undergo rapid cellular division. As they are actively dividing, the bacterial cells are lysed and their DNA is extracted and purified. Analysis of the partially replicated DNA fragments shows the presence of uracil. This finding is most likely mediated by which of the following enzymes?

- A. DNA ligase
- B. DNA polymerase I
- C. DNA polymerase III
- D. Gyrase
- E. Helicase
- F. Primase

Submit

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- A. DNA ligase (2%)
- B. DNA polymerase I (15%)
- C. DNA polymerase III (18%)
- D. Gyrase (2%)
- E. Helicase (1%)
- ✓ F. Primase (59%)

Omitted
Correct answer
F

59%
Answered correctly

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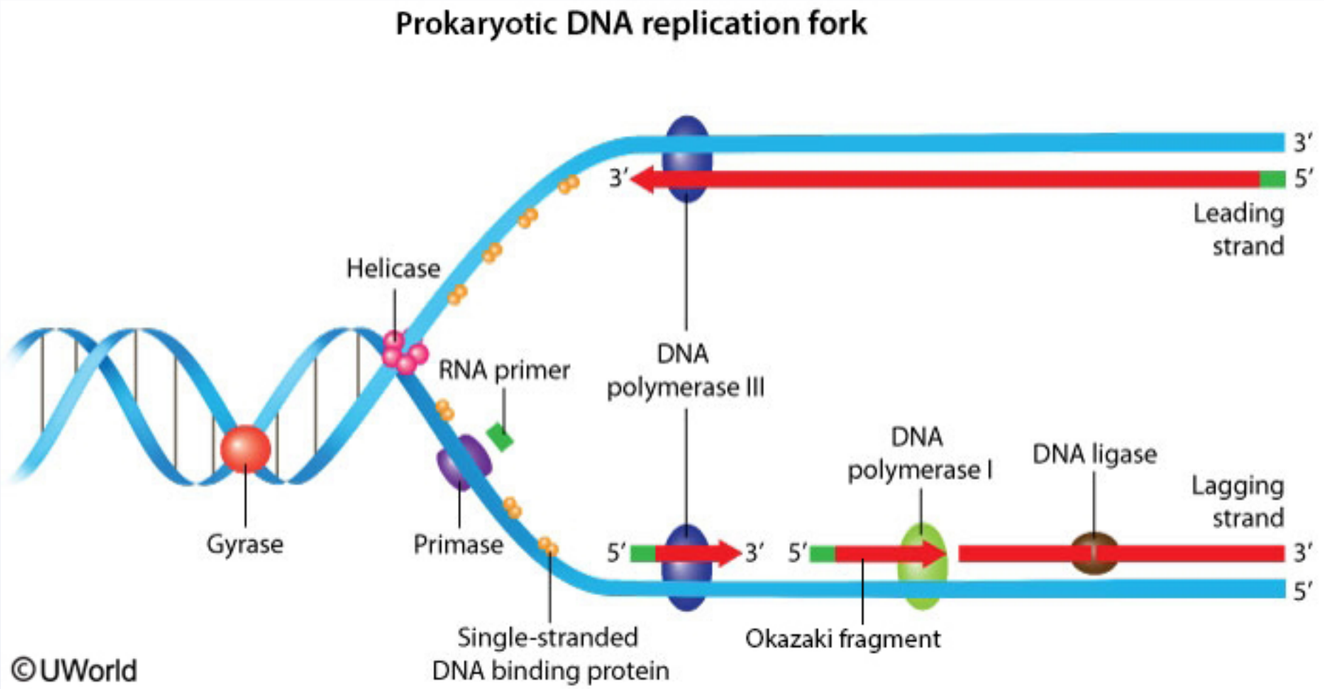
Explanation

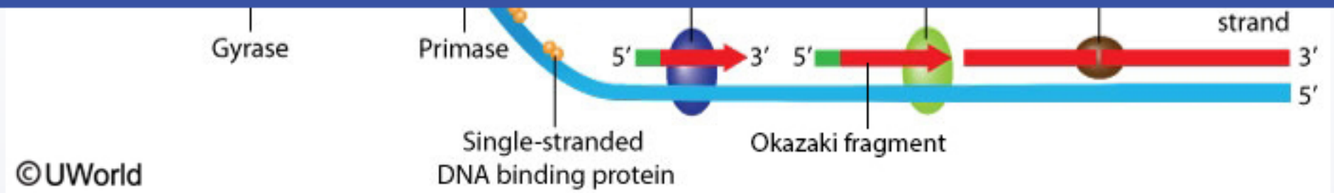
Prokaryotic DNA replication fork



This question describes a scenario in which uracil is found in association with bacterial DNA during prokaryotic DNA replication. In general, uracil is found only in RNA, so the question essentially asks which enzyme involved in DNA synthesis catalyzes the formation of RNA strands. In prokaryotic DNA replication, primase (an RNA polymerase) is responsible for synthesizing a short RNA primer using the separated strands of DNA at the replication fork as templates. DNA replication then proceeds, with DNA polymerase using the 3' hydroxyl group of the RNA primer as a starting point for synthesis. Primase is a crucial enzyme for bacterial replication as DNA polymerase cannot initiate DNA synthesis without this short nucleic acid sequence primer.

(Choice A) DNA ligase is the enzyme that repairs single-strand breaks in duplex DNA during DNA replication and repair.

(Choices B and C) During replication, DNA polymerase III is the primary enzyme responsible for synthesis of daughter DNA strands; DNA polymerase I functions chiefly to replace the RNA primers with DNA segments. Unlike DNA polymerase III, DNA polymerase I has 5'→ 3'



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(Choice A) DNA ligase is the enzyme that repairs single-strand breaks in duplex DNA during DNA replication and repair.

(Choices B and C) During replication, DNA polymerase III is the primary enzyme responsible for synthesis of daughter DNA strands; DNA polymerase I functions chiefly to replace the RNA primers with DNA segments. Unlike DNA polymerase III, DNA polymerase I has 5'→ 3' exonuclease activity that can remove RNA primers and damaged DNA segments. The 3'→ 5' exonuclease activity of DNA polymerase I and III provides a proofreading function that fixes mismatched nucleotides in the newly formed daughter strands.

(Choices D and E) Helicase unwinds DNA at the replication fork. However, this process results in supercoiling of the DNA. DNA gyrase is a type II topoisomerase that helps to relieve the resultant strain.

Educational objective:
Primase is a DNA-dependent RNA polymerase that incorporates short RNA primers into replicating DNA.

Biochemistry	Renal, Urinary Systems & Electrolytes	Transcription
Subject	System	Topic

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A 24-year-old man comes to emergency department complaining of abdominal pain, vomiting, and severe watery diarrhea. He recently returned from a camping trip and admits to eating wild mushrooms that he collected in the woods. His past medical history is insignificant and he takes no medications. He does not use illicit drugs. On physical examination, he is ill-appearing and jaundiced. His liver edge is soft, tender, and palpable 4 cm below the right costal margin. Laboratory tests are significant for elevated levels of alanine aminotransferase, aspartate aminotransferase, and bilirubin. Synthesis of which of the following is most likely to be directly inhibited by the responsible toxin?

- A. DNA
- B. Messenger RNA
- C. Protein
- D. Ribosomal RNA
- E. Transfer RNA

Submit

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- A. DNA (6%)
- ✓ B. Messenger RNA (42%)
- C. Protein (28%)
- D. Ribosomal RNA (19%)
- E. Transfer RNA (3%)

Omitted
Correct answer
B

42%
Answered correctly

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Time Spent

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Last Updated

Explanation

Eukaryotic RNA polymerase	Major RNA product
RNA polymerase I	Ribosomal RNA

Eukaryotic RNA polymerase	Major RNA product
RNA polymerase I	Ribosomal RNA
RNA polymerase II	Messenger RNA
RNA polymerase III	Transfer RNA

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Amatoxins are found in a variety of poisonous mushrooms (eg, *Amanita phalloides*, known as death cap) and are responsible for the majority of mushroom poisoning fatalities worldwide. Ingestion of 1 or more amatoxin-containing mushrooms is a life-threatening emergency. After absorption by the gastrointestinal tract, amatoxins are transported to the liver via the portal circulation where active transport by organic anion transporting polypeptide (OATP) and sodium taurocholate co-transporter (NTCP) concentrates the toxin within the liver cells. There, amatoxins bind to DNA-dependent RNA polymerase type II and halt mRNA synthesis, ultimately resulting in apoptosis. Other organ systems with rapid cellular turnover can also be affected in amatoxin poisoning, including the gastrointestinal tract and proximal convoluted renal tubules.

Symptoms typically start 6-24 hours after ingestion and include abdominal pain, vomiting, and severe, cholera-like diarrhea that may contain blood and mucus. Severe poisoning can lead to acute hepatic and renal failure. Urine testing for α-amanitin can confirm suspected amatoxin poisoning.

(Choice A) Acyclovir and related drugs (eg, famciclovir and valacyclovir) are inhibitors of viral DNA polymerase.

(Choice C) Ricin (from the castor oil plant *Ricinus communis*) is a potent toxin that inhibits protein synthesis by cleaving the rRNA component of the eukaryotic 60S subunit.

(Choice D) The only function of RNA polymerase I is to transcribe the majority of the eukaryotic ribosomal RNA components. RNA polymerase I is insensitive to amatoxins.

(Choice E) Eukaryotic RNA polymerase III transcribes transfer RNA, 5S ribosomal RNA, and other small RNA molecules. It is only weakly affected by amatoxins.

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(Choice E) Eukaryotic RNA polymerase III transcribes transfer RNA, 5S ribosomal RNA, and other small RNA molecules. It is only weakly affected by amatoxins.

Educational objective:
Amatoxins are found in a variety of poisonous mushrooms (eg, *Amanita phalloides*, known as death cap) and are potent inhibitors of RNA polymerase II (halting mRNA synthesis).

References

- Amatoxins, phallotoxins, phallolysin, and antamanide: the biologically active components of poisonous Amanita mushrooms.
- Treatment of amatoxin poisoning: 20-year retrospective analysis.

Biochemistry	Poisoning & Environmental Exposure	Mushroom poisoning
Subject	System	Topic

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A 14-month-old boy is evaluated for failure to thrive and developmental delay. His mother reports that at 12 months he could barely lift his head and had difficulty sitting unsupported. The toddler has not started babbling or forming words. He is at the 10th percentile for height and 5th percentile for weight. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Mean corpuscular volume	114 fL
Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

A. Ascorbic acid
B. Folic acid
C. Guanine
D. Iron
E. Pyridoxine
F. Uridine

Submit

A 14-month-old boy is evaluated for failure to thrive and developmental delay. His mother reports that at 12 months he could barely lift his head and had difficulty sitting unsupported. The toddler has not started babbling or forming words. He is at the 10th percentile for height and 5th percentile for weight. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Mean corpuscular volume	114 fL
Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

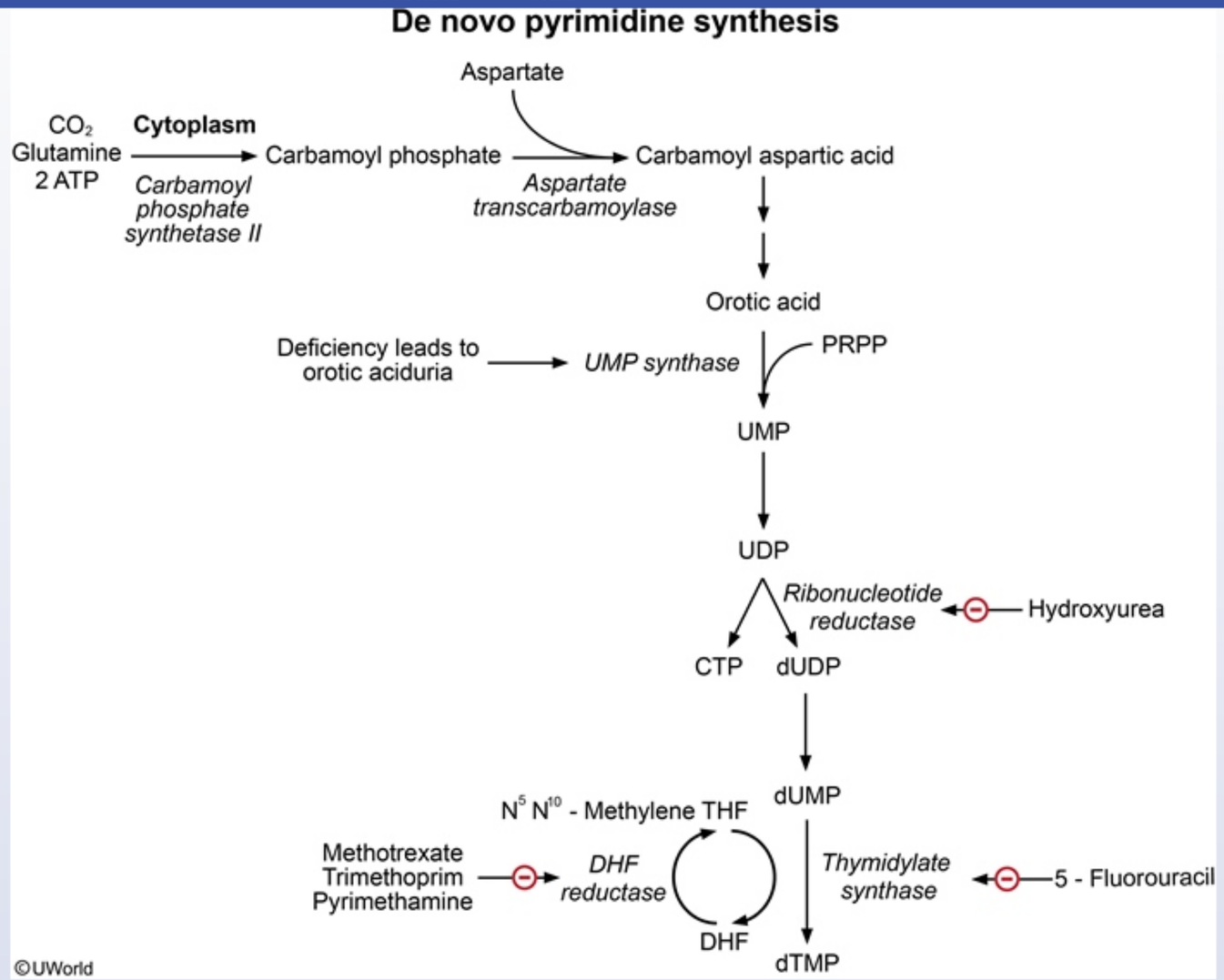
A. Ascorbic acid (2%)
B. Folic acid (26%)
C. Guanine (5%)
D. Iron (1%)
E. Pyridoxine (23%)
✓ F. Uridine (40%)

Omitted
Correct answer
F

40%
Answered correctly

41 secs
Time Spent

06/20/2020
Last Updated



This patient likely has **hereditary orotic aciduria**, a rare autosomal recessive disorder of de novo pyrimidine synthesis that results in **physical and mental retardation** (eg, low height/weight, delayed developmental milestones), **megaloblastic anemia** (eg, elevated mean corpuscular

This patient likely has **hereditary orotic aciduria**, a rare autosomal recessive disorder of de novo pyrimidine synthesis that results in **physical and mental retardation** (eg, low height/weight, delayed developmental milestones), **megaloblastic anemia** (eg, elevated mean corpuscular volume, low reticulocyte count), and **elevated urinary orotic acid** levels. Increased urinary orotic acid may also be seen in ornithine transcarbamylase deficiency; however, patients with this condition classically have failure to thrive and hyperammonemic encephalopathy within the first few weeks of life (due to impaired urea synthesis).

Hereditary orotic aciduria occurs due to a **defect** in **uridine 5'-monophosphate (UMP) synthase**, a polypeptide containing 2 enzymatic domains (orotate phosphoribosyltransferase and OMP decarboxylase) that catalyze the final conversion of orotic acid to UMP. Impaired conversion of orotic acid to UMP results in the excretion of large amounts of orotic acid in the urine and the clinical features described above. **Uridine supplementation** can bypass this enzymatic defect and improve symptoms as uridine is converted to UMP via nucleoside kinases.

(Choice A) Ascorbic acid (vitamin C) is required for hydroxylation of proline and lysine residues in collagen synthesis; therefore, it plays an important role in connective tissue maintenance and wound healing.

(Choice B) Folate participates in single carbon transfer reactions, as in the de novo synthesis of purines and thymidine. Folate supplements will improve megaloblastic anemia resulting from folate deficiency but will not improve the anemia in orotic aciduria.

(Choice C) Guanine and adenine are purine bases present in DNA and RNA. Orotic aciduria is a defect in the synthesis of pyrimidine bases, so supplementation with purines would not affect orate synthesis.

(Choice D) Iron supplementation improves iron deficiency anemia, classically a microcytic hypochromic anemia.

(Choice E) Pyridoxine (vitamin B_6) supplementation is indicated during treatment with isoniazid. Pyridoxine is a cofactor in transamination, deamination, decarboxylation, and condensation reactions.

Educational objective:
Orotic aciduria is a rare autosomal recessive disorder of de novo pyrimidine synthesis that occurs due to a defect in uridine 5'-monophosphate (UMP) synthase. Children typically present with physical and mental retardation, megaloblastic anemia, and large amounts of urinary orotic acid. Uridine supplementation can improve symptoms as uridine is converted to UMP via nucleoside kinases.

References

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References

- Orotic aciduria and uridine monophosphate synthase: a reappraisal.
- Inborn errors of pyrimidine metabolism: clinical update and therapy.

Biochemistry	Endocrine, Diabetes & Metabolism	Protein synthesis
Subject	System	Topic

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A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower quadrant abdominal pain approximately 30 hours earlier but did not go to the hospital because she thought the pain would subside on its own. The patient had no food, only sips of water, during that time. Blood pressure is 115/72 mm Hg and pulse is 106/min. Mucous membranes are dry and there is tenderness in the right lower quadrant of the abdomen. Laboratory evaluation shows mild leukocytosis, normal serum electrolytes, borderline low serum glucose levels, and moderate ketones in the urine. Based on the evaluation, it is suspected that this patient is utilizing ketone bodies as a significant reserve of energy. Which of the following tissues cannot use this energy source?

A. Brain
B. Erythrocytes
C. Heart muscle
D. Renal cortex
E. Skeletal muscle

Submit

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- A. Brain (13%)
- ✓ B. Erythrocytes (79%)
- C. Heart muscle (1%)
- D. Renal cortex (1%)
- E. Skeletal muscle (4%)

Omitted
Correct answer
B

79%
Answered correctly

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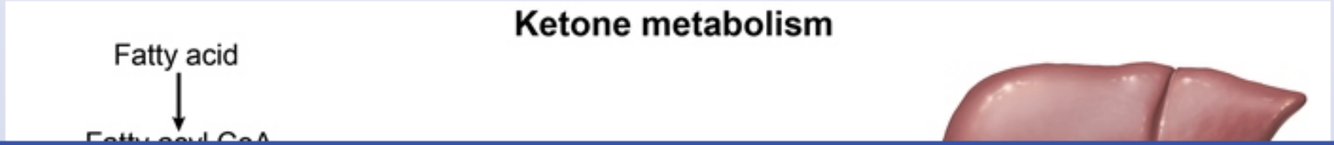
Last Updated

Explanation



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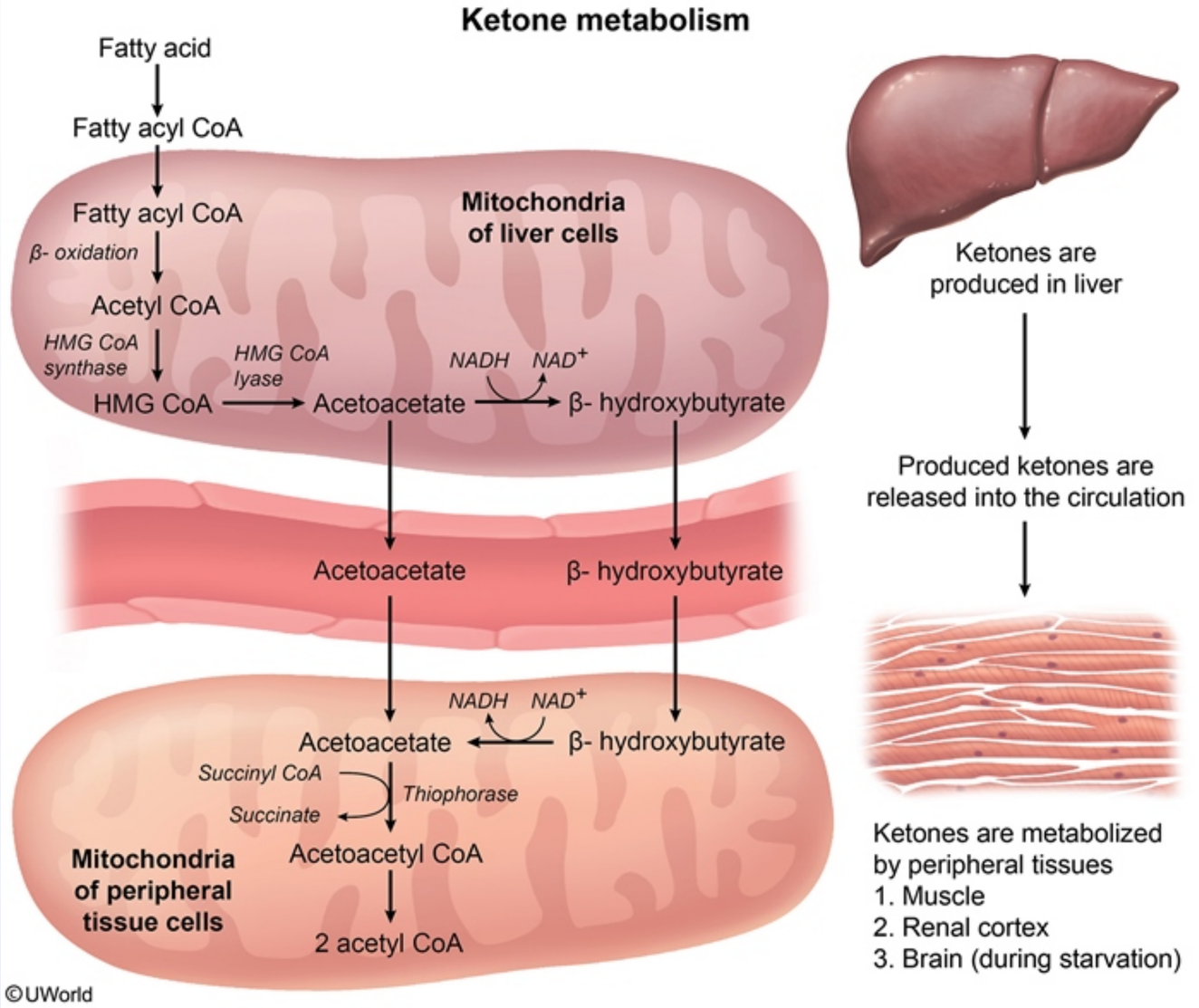

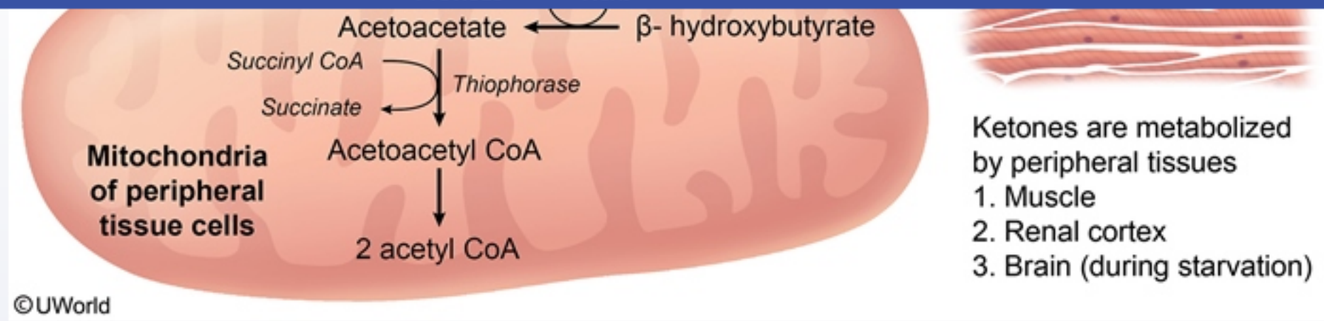

After about 12-18 hours of **fasting**, the body's glycogen stores are depleted and **gluconeogenesis** is required to maintain blood glucose levels. As fasting continues, the body limits its reliance on gluconeogenesis in an effort to conserve protein and resorts instead to **ketone body synthesis**. Ketone bodies are generated in the liver from fatty acids and yield energy when converted to acetyl CoA in the **mitochondria** of target cells.

The brain, kidneys, cardiac muscle, and skeletal muscle **(Choices A, C, D & E)** can all utilize ketones for energy. In the initial stages of fasting, the heart and skeletal muscle consume primarily ketone bodies to preserve glucose for the brain, but in prolonged starvation, even the brain will utilize ketone bodies for the majority of its energy needs. However, erythrocytes cannot use ketone bodies for energy because they lack mitochondria. The liver is also unable to utilize ketone bodies for energy because it lacks the enzyme succinyl CoA-acetoacetate CoA transferase (thiophorase), which is required to convert acetoacetate to acetoacetyl CoA.

Educational objective:
When glycogen stores are depleted during fasting, ketone bodies are produced in the liver and can be used as an energy source in the mitochondria of peripheral tissues. The brain preferentially uses glucose, but will utilize ketones for most of its energy needs during prolonged starvation. Erythrocytes lack mitochondria and are unable to use ketones.

Biochemistry	Endocrine, Diabetes & Metabolism	Gluconeogenesis
Subject	System	Topic

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An 8-year-old boy is brought to the emergency department due to vomiting and lethargy. The patient had been on an overnight hiking trip with his family. During the trip, the family lost their food pack while canoeing and had to hike back to their car. The child became weak and was carried for the last mile. None of the family has eaten for approximately 24 hours. On examination, the patient appears listless. Mild hepatomegaly is noted. Laboratory results are as follows:

Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

A. Acetyl-CoA carboxylase
B. Acid alpha-glucosidase
C. Acyl-CoA dehydrogenase
D. Glucose 6-phosphatase
E. Glycogen phosphorylase

Submit

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Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

A. Acetyl-CoA carboxylase (15%)
B. Acid alpha-glucosidase (3%)
✓ C. Acyl-CoA dehydrogenase (34%)
D. Glucose 6-phosphatase (25%)
E. Glycogen phosphorylase (21%)

Omitted
Correct answer
C

34%
Answered correctly

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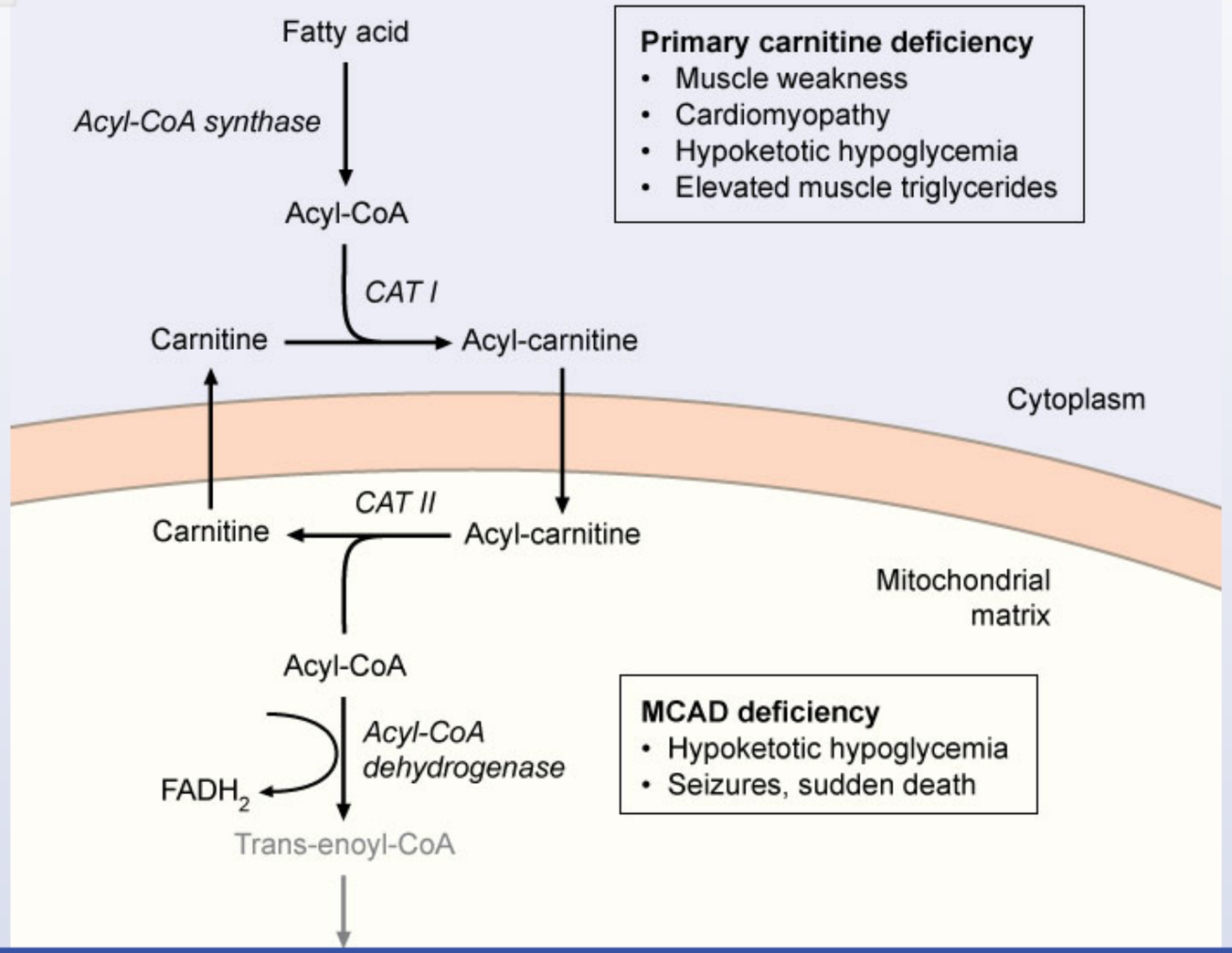
Last Updated

Magn... Views

Fatty acid oxidation



Primary carnitine deficiency
- Muscle weakness
- Cardiomyopathy
- Hypoketotic hypoglycemia
- Elevated muscle triglycerides

MCAD deficiency
- Hypoketotic hypoglycemia
- Seizures, sudden death

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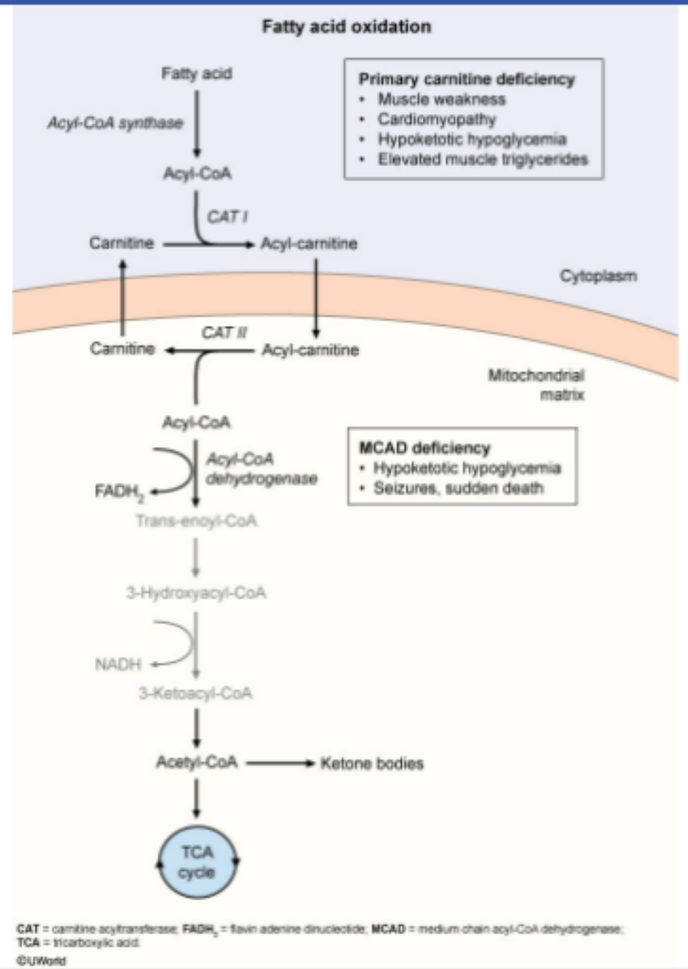

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This patient developed **hypoketotic hypoglycemia** after fasting, which is consistent with a **defect in fatty acid beta-oxidation** in the mitochondria. Beta-oxidation of fatty acids yields $FADH_2$ and NADH for ATP production and generates acetyl-CoA for use in the citric acid cycle or ketone body production. **Ketone bodies** are an important energy source during periods of fasting; adults generally require more than 1-2 days of fasting before ketone use becomes substantial, whereas children have limited glucose reserves and begin using ketone bodies after as little as 8-10 hours.

Impaired beta-oxidation can be caused by a variety of enzymatic defects, the most common of which is **medium chain acyl-CoA dehydrogenase deficiency**. Affected individuals may remain asymptomatic for long periods until they experience a **significant fast**, during which they are unable to oxidize fatty acids to maintain glucose and ketone body production. Classic manifestations include hypoketotic hypoglycemia (eg, undetectable acetoacetate level), mild hepatomegaly, and liver dysfunction. Because the resulting metabolic crisis can have severe consequences (eg, seizures, sudden infant death), fatty acid oxidation disorders are part of standard newborn screening.

Treatment of acyl-CoA dehydrogenase deficiency consists of prevention of fat catabolism. This means avoiding prolonged fasting as well as promptly supplying **glucose** during periods of illness.

(Choice A) Acetyl-CoA carboxylase is the rate-limiting enzyme that catalyzes the first step in fatty acid synthesis. Acetyl-CoA carboxylase is normally suppressed during prolonged fasting.

(Choices B, D, and E) Acid alpha-glucosidase, glucose 6-phosphatase, and glycogen phosphorylase are involved in glycogenolysis. Deficiency of any of these enzymes can lead to glycogen storage disease. However, patients with glycogen storage disease have normal fatty acid oxidation and produce ketones during periods of fasting.

Educational objective:
Impaired beta-oxidation of fatty acids causes hypoglycemia after prolonged fasting and insufficient levels of ketone bodies. Acyl-CoA dehydrogenase catalyzes the first step in the beta-oxidation pathway and is the most commonly deficient enzyme.

References

- Newborn screening for medium chain acyl CoA dehydrogenase deficiency.
- Ketone body transport in the human neonate and infant.

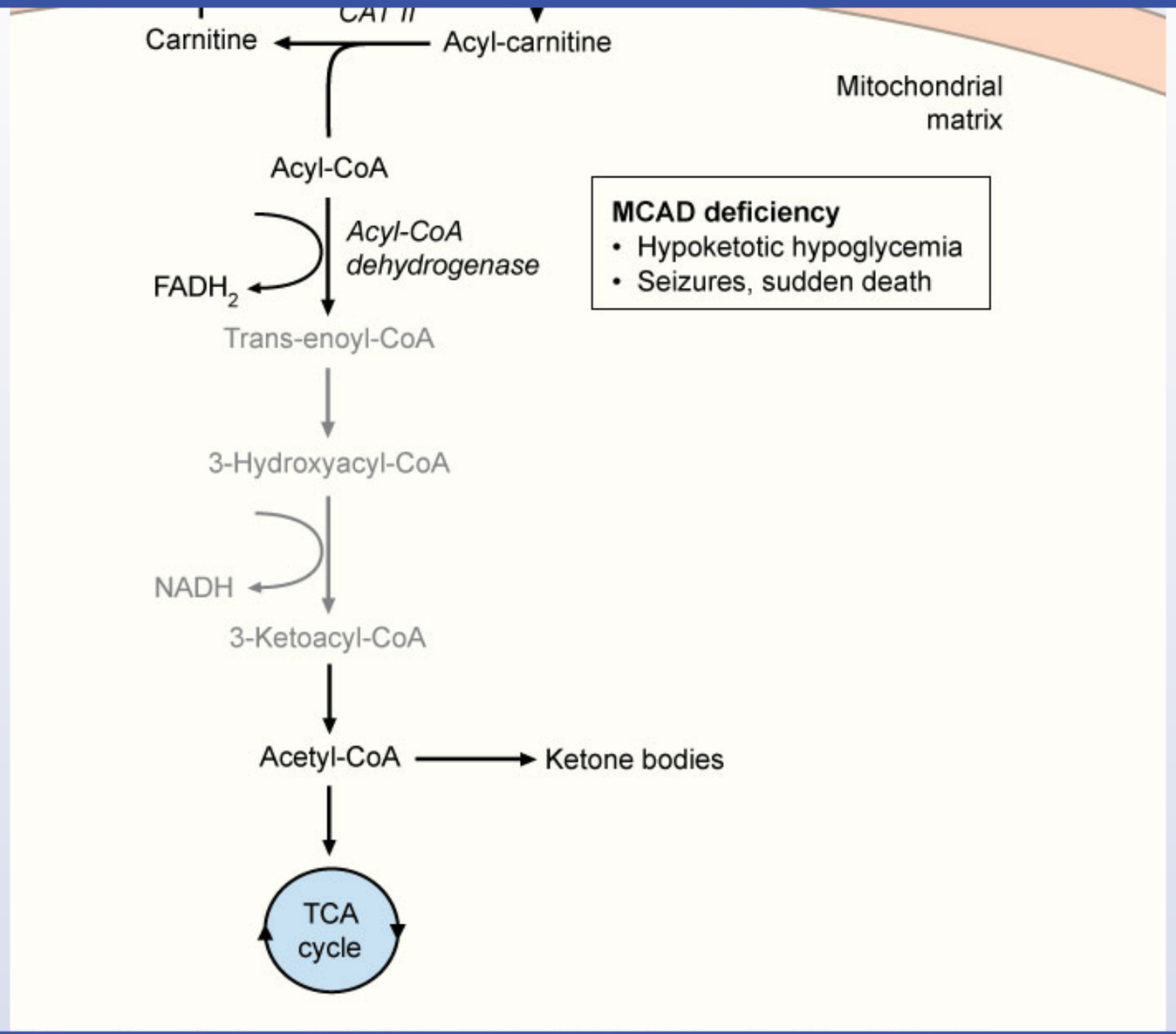
CAT II
Carnitine
Acyl-carnitine
Mitochondrial matrix
Acyl-CoA
Acyl-CoA dehydrogenase
FADH2
Trans-enoyl-CoA
3-Hydroxyacyl-CoA
NADH
3-Ketoacyl-CoA
Acetyl-CoA
Ketone bodies
TCA cycle
MCAD deficiency
• Hypoketotic hypoglycemia
• Seizures, sudden death

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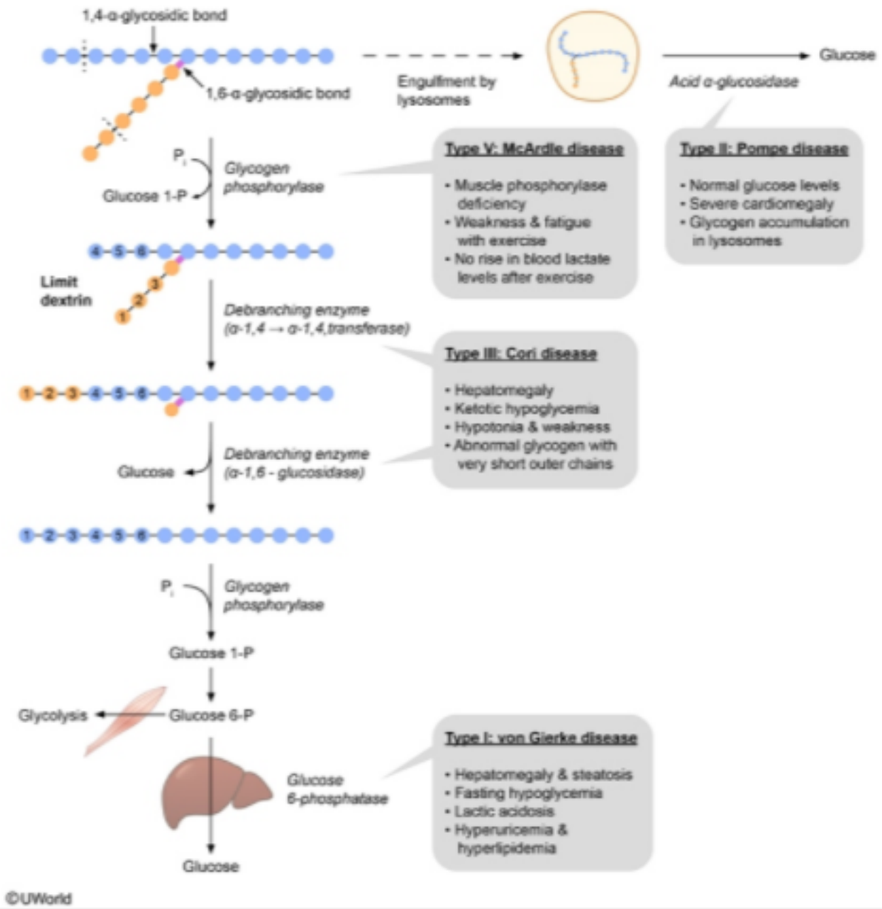
Exhibit Display

Impairments in glycogenolysis



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A group of investigators is studying the regulation of catecholamine synthesis in response to severe stress. In the experiments, subject rats are randomly assigned to either an experimental or a control group. The experimental rats undergo resection of the pituitary gland, and the control rats undergo craniotomy without pituitary resection. The experimental animals are subsequently found to have decreased production of epinephrine by the adrenal medulla and cortisol from the adrenal cortex compared with the control animals. Decreased activity of which of the following enzymes is most likely responsible for the lower epinephrine in the experimental animals?

- A. Catechol-O-methyl transferase
- B. Dopa decarboxylase
- C. Dopamine beta-hydroxylase
- D. Monoamine oxidase
- E. Phenylalanine hydroxylase
- F. Phenylethanolamine-N-methyltransferase
- G. Tyrosine hydroxylase

Submit

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- A. Catechol-O-methyl transferase (13%)
- B. Dopa decarboxylase (11%)
- C. Dopamine beta-hydroxylase (16%)
- D. Monoamine oxidase (4%)
- E. Phenylalanine hydroxylase (3%)
- ✓ F. Phenylethanolamine-N-methyltransferase (41%)
- G. Tyrosine hydroxylase (10%)

Omitted
Correct answer
F

41%
Answered correctly

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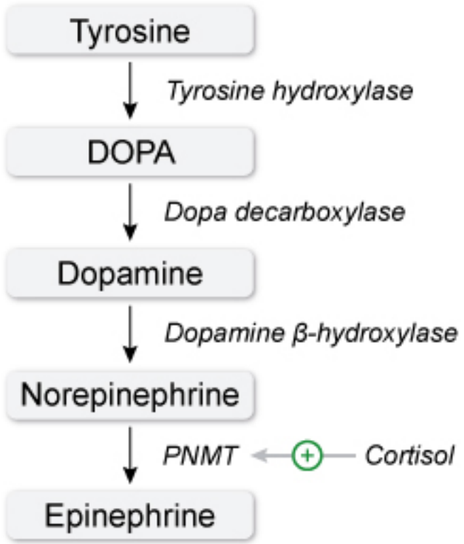
Explanation

Catecholamine synthesis

Catecholamine synthesis



PNMT = phenylethanolamine-N-methyltransferase.
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The 3 main circulating catecholamines are dopamine, norepinephrine, and epinephrine. Norepinephrine and dopamine are produced in the central as well as the peripheral nervous system, whereas epinephrine is predominantly produced in the **adrenal medulla**. The first step in the synthesis of catecholamines is the conversion of tyrosine to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the synthesis of catecholamines. DOPA is converted to dopamine by dopa decarboxylase **(Choice B)**, which is then converted to norepinephrine by dopamine beta-hydroxylase **(Choice C)**. In the adrenal medulla, norepinephrine is rapidly converted to epinephrine by **phenylethanolamine-N-methyltransferase** (PNMT).

Expression of PNMT in the adrenal medulla is upregulated by cortisol. Because the venous drainage of the adrenal cortex passes through the adrenal medulla, cortisol concentrations in the medulla can be very high, and PNMT is expressed at a high level. However, following **pituitary resection**, the loss of ACTH leads to decreased synthesis of cortisol in the adrenal cortex. The result is **decreased PNMT activity** and reduced conversion of norepinephrine to epinephrine.

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(Choices A and D) Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO) are responsible for inactivation of catecholamines. COMT converts epinephrine to metanephrine and norepinephrine to normetanephrine; MAO converts metanephrine and normetanephrine to vanillylmandelic acid.

(Choices E and G) Tyrosine required for the synthesis of catecholamines is obtained from either dietary intake or by conversion of phenylalanine by phenylalanine hydroxylase in the liver. Deficiency of phenylalanine hydroxylase enzyme causes phenylketonuria. Tyrosine hydroxylase deficiency impairs catecholamine synthesis and causes infantile parkinsonism and progressive encephalopathy.

Educational objective:
Cortisol increases the conversion of norepinephrine to epinephrine in the adrenal medulla by increasing the expression of phenylethanolamine-N-methyltransferase.

References

- Stress-triggered changes in peripheral catecholaminergic systems.

Biochemistry	Endocrine, Diabetes & Metabolism	Pheochromocytoma
Subject	System	Topic

A 17-year-old boy who was recently diagnosed with type 1 diabetes mellitus is found unresponsive at home. His family reports that the patient did not feel good last night and skipped dinner, but he still took his usual dose of insulin. Paramedics find that his fingerstick blood glucose is 32 mg/dL and immediately administer intramuscular glucagon. Glucagon binds to a transmembrane receptor in hepatocytes, which promotes binding of intracellular GTP to a specific receptor-associated protein. This leads to further downstream signaling and rapid metabolic changes within hepatocytes, including a rapid decrease in intracellular glycogen stores and release of glucose into the blood. Which of the following is the most likely mediator responsible for these effects?

A. cGMP-dependent protein kinase

B. Janus tyrosine kinase

C. Phosphodiesterase

D. Protein kinase A

E. Tyrosine-specific protein kinase

Submit

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- A. cGMP-dependent protein kinase (18%)
- B. Janus tyrosine kinase (6%)
- C. Phosphodiesterase (3%)
- ✓ D. Protein kinase A (61%)
- E. Tyrosine-specific protein kinase (10%)

Omitted
Correct answer
D

61%
Answered correctly

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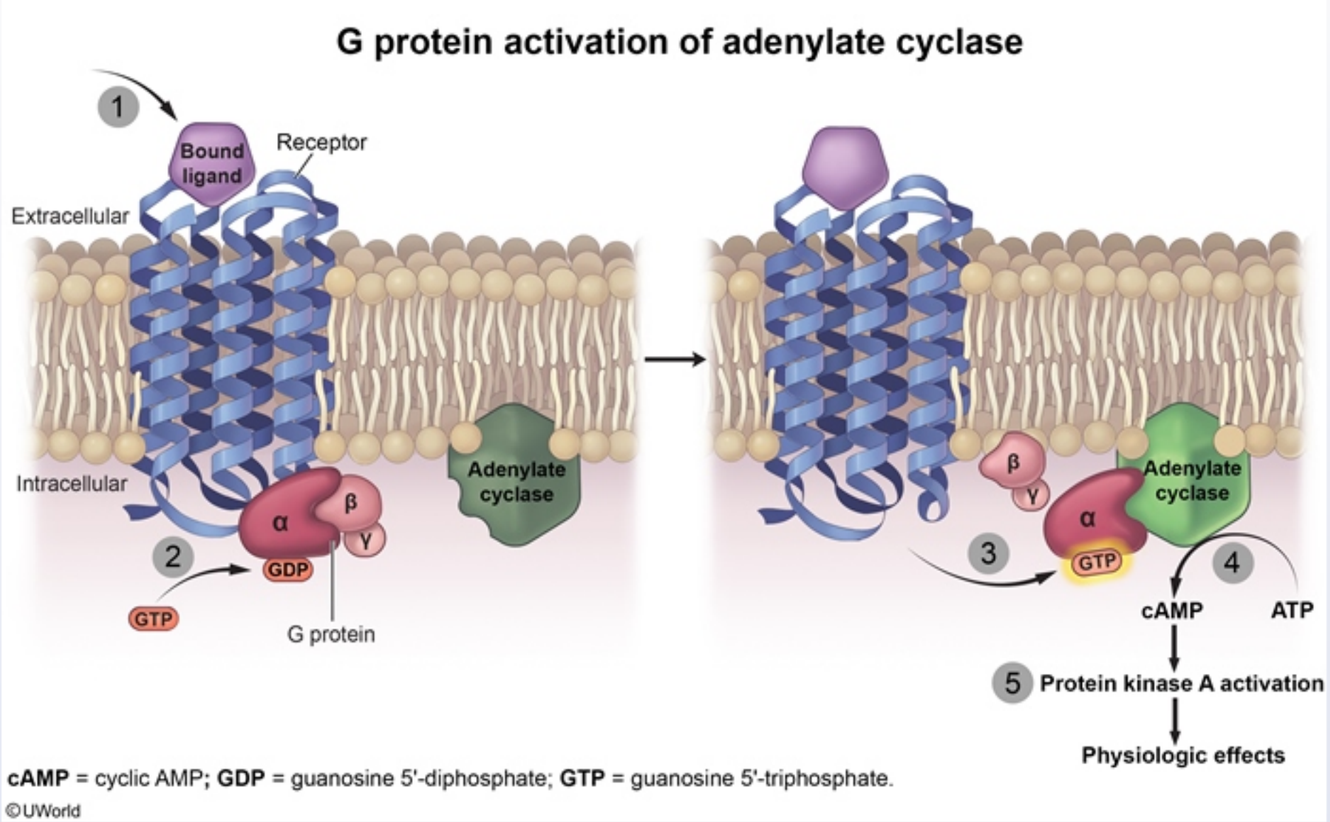
Explanation



Glucagon exerts its effects through G protein-coupled receptors using the **adenylate cyclase second messenger system**. G protein is a heterotrimer consisting of alpha, beta, and gamma subunits associated with the intracellular domain of these transmembrane receptors. The alpha subunit of the inactivated G protein is bound to GDP. On **receptor activation**, the alpha subunit undergoes a conformational change, which releases GDP and binds GTP. **GTP binding** allows the alpha subunit to dissociate from the remainder of the G protein complex.

There are multiple subtypes of alpha G proteins, each with different secondary effects. A specific alpha subunit known as $\mathbf{G_s}$ (present in glucagon, TSH, and PTH receptor complexes) **activates adenylate cyclase** when released from the G protein complex. Adenylate cyclase converts ATP to

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(Choice A) cGMP activates protein kinase G, which mediates a number of intracellular effects (eg, smooth muscle relaxation, platelet activation, sperm metabolism). cGMP is inactivated by cGMP phosphodiesterase, which cleaves cGMP in the corpus cavernosum of the penis and regulates penile erection. Drugs that inhibit cGMP-specific phosphodiesterase (eg, sildenafil) are used in the treatment of erectile dysfunction.

(Choice B) Janus tyrosine kinase (JAK) is a cytoplasmic protein activated by ligand binding to non-G protein-coupled transmembrane receptors that lack intrinsic tyrosine kinase activity. Growth hormone, erythropoietin, and cytokines (eg, interferon) are common ligands for these receptors. JAKs activate cytoplasmic transcription factors called STATs (signal transducers and activators of transcription), which enter the nucleus to promote gene transcription.

(Choice C) cAMP is cleaved by the enzyme cAMP phosphodiesterase to its inactive form, 5'-AMP. Drugs that inhibit cAMP phosphodiesterase lead to prolongation of the actions of cAMP. An example is the use of theophylline in bronchial asthma.

(Choice E) Ligands such as insulin and epidermal growth factor act through transmembrane receptors that have intrinsic tyrosine kinase domains.

Educational objective:
Protein kinase A is responsible for the intracellular effects of the G protein-mediated adenylate cyclase second messenger system. Hormone receptors that use this system include the TSH, glucagon, and PTH receptors.

References

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References

- Glucagon receptors.

Biochemistry	Endocrine, Diabetes & Metabolism	Second messengers
Subject	System	Topic

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TSH, and PTH receptor complexes) **activates adenylate cyclase** when released from the G protein complex. Adenylate cyclase converts ATP to

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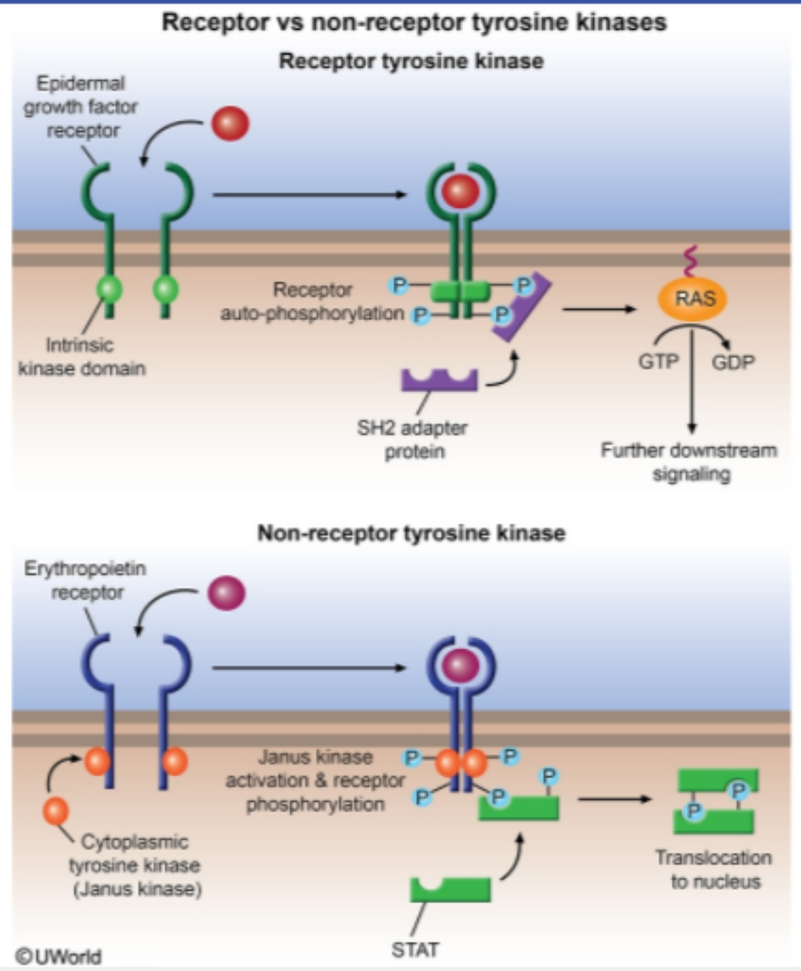

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An 8-year-old boy is evaluated for exercise intolerance. The patient experiences fatigue, muscle pain, and cramps during exercise as well as severe muscle stiffness following strenuous activity. Physical examination is unremarkable. A forearm ischemic exercise test is performed by applying a blood pressure cuff on the patient's exercising forearm and sampling blood lactate several minutes after the exercise. The patient's blood samples show no rise in lactate levels. Biochemical analysis of a muscle biopsy reveals absent lactate dehydrogenase activity. In this patient, strenuous exercise leads to inhibition of glycolysis in skeletal muscle due to intracellular depletion of which of the following substances?

- A. AMP
- B. Carnitine
- C. Citrate
- D. $FADH_2$
- E. NAD^+
- F. Pyruvate

Submit

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- A. AMP (6%)
- B. Carnitine (3%)
- C. Citrate (3%)
- D. $FADH_2$ (2%)
- ✓ E. NAD^+ (64%)
- F. Pyruvate (18%)

Omitted
Correct answer
E

64%
Answered correctly

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03/16/2020
Last Updated

Explanation

Glucose

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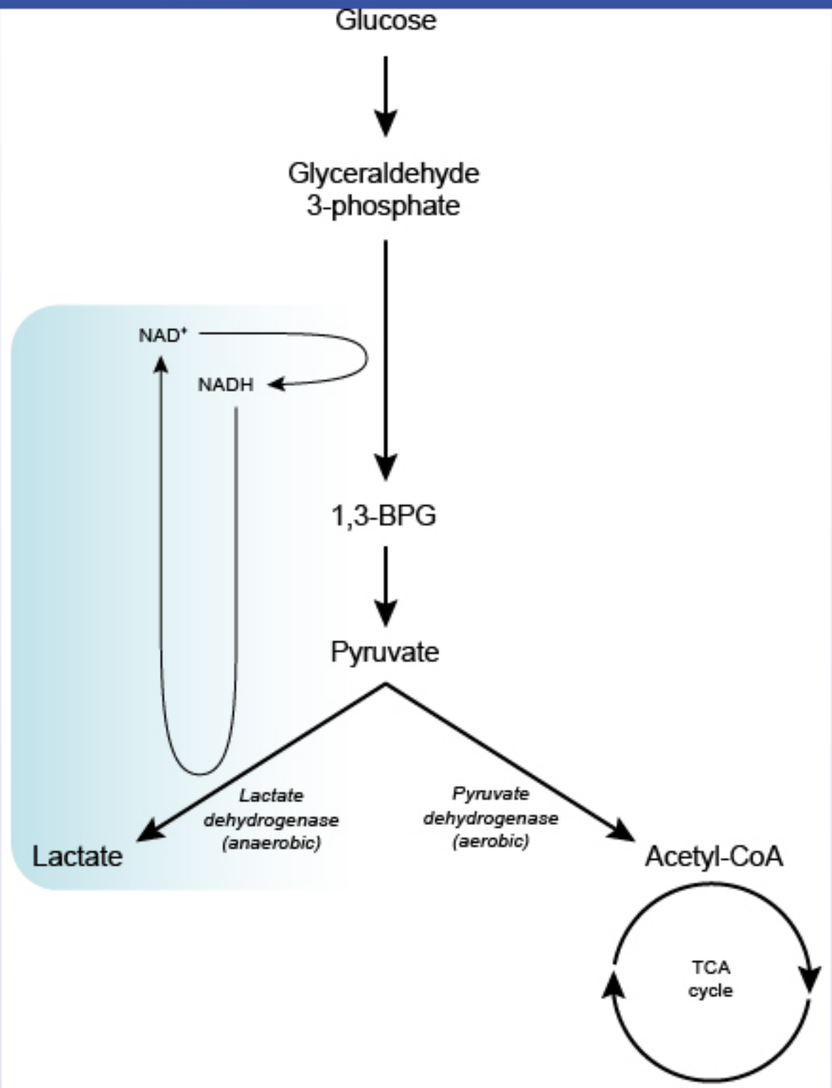

1,3-BPG = 1,3-bisphosphoglyceric acid.

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In glycolysis, glucose is metabolized to pyruvate. Under aerobic conditions, pyruvate is converted to acetyl-CoA to enter the tricarboxylic acid

In glycolysis, glucose is metabolized to pyruvate. Under aerobic conditions, pyruvate is converted to acetyl-CoA to enter the tricarboxylic acid (TCA) cycle. When oxygen is depleted (eg, in exercising muscle), pyruvate is converted to lactate (**anaerobic glycolysis**).

During glycolysis, glyceraldehyde-3-phosphate (G3P) is converted to 1-3-bisphosphoglycerate (BPG) by the enzyme G3P dehydrogenase. This enzyme reduces NAD^+ to NADH. NAD^+ is present in limited amounts in most cells, and it must be regenerated from NADH for glycolysis to continue. Under aerobic conditions, NAD^+ is converted to NADH in the TCA cycle. NADH is then reconverted to NAD^+ in the electron transport chain as the energy in NADH is utilized to synthesize ATP.

In anaerobic glycolysis, **NAD+** is **regenerated** from NADH when pyruvate is converted to lactate via **lactate dehydrogenase**. In patients with lactate dehydrogenase deficiency, glycolysis is inhibited in strenuously exercising muscle as muscle cells cannot regenerate NAD^+. Consequently, high-intensity physical activity leads to muscle breakdown, pain, and fatigue as insufficient amounts of energy are being produced in the exercising muscle.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of glycogen phosphorylase, which activates this enzyme. Non-phosphorylation-dependent activation of glycogen phosphorylase can occur during muscle contraction via increased intracellular calcium concentrations and via AMP under extreme conditions.

(Choice B) Carnitine is an amino acid derivative responsible for transporting fatty acids into the mitochondria for beta-oxidation. Carnitine is synthesized from lysine and methionine; vitamin C is essential for this synthesis.

(Choice C) Citrate is formed from the condensation of acetyl CoA with oxaloacetate in the first step of the TCA cycle. Increased citrate concentrations decrease glycolysis as citrate is a powerful allosteric inhibitor of phosphofructokinase-1. In exercising muscles under anaerobic conditions, oxidative phosphorylation of glucose through the citric acid cycle is not a dominant pathway; therefore, excess citrate is not produced.

(Choice D) $FADH_2$ is not produced in glycolysis. $FADH_2$ is produced from FAD during the conversion of succinate to fumarate in the TCA cycle by the enzyme succinate dehydrogenase.

(Choice F) In glycolysis, pyruvate is formed from phosphoenolpyruvate by a unidirectional enzyme called pyruvate kinase. In the absence of lactate dehydrogenase activity, pyruvate will accumulate in the cell under anaerobic conditions.

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Educational objective:
Under anaerobic conditions, NADH transfers electrons to pyruvate to form lactate and regenerate NAD^+. NAD^+ is required to convert glyceraldehyde-3-phosphate to 1-3-bisphosphoglycerate in glycolysis.

References

- Lactate dehydrogenase M-subunit deficiencies: clinical features, metabolic background, and genetic heterogeneities.

Biochemistry	Endocrine, Diabetes & Metabolism	Glycolysis
Subject	System	Topic

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A 35-year-old woman comes to the emergency department with nausea, vomiting, and fever. Her symptoms began 24 hours ago, and she has been unable to eat or drink anything since. She has a 3-year-old daughter who had similar symptoms 2 days earlier but is now fine. Laboratory studies show a blood glucose level of 82 mg/dL despite her 24-hour fast. Maintenance of this patient's blood glucose levels is facilitated by hepatic conversion of pyruvate into glucose. Which of the following substances directly stimulates the first enzyme involved in this process?

- A. Acetyl-CoA
- B. Alanine
- C. Citrate
- D. Fructose 2,6-bisphosphate
- E. Lactate
- F. Oxaloacetate

Submit

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- ✓ A. Acetyl-CoA (39%)
- B. Alanine (7%)
- C. Citrate (12%)
- D. Fructose 2,6-bisphosphate (17%)
- E. Lactate (6%)
- F. Oxaloacetate (16%)

Omitted
Correct answer
A

39%
Answered correctly

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Explanation

Metabolic fate of pyruvate

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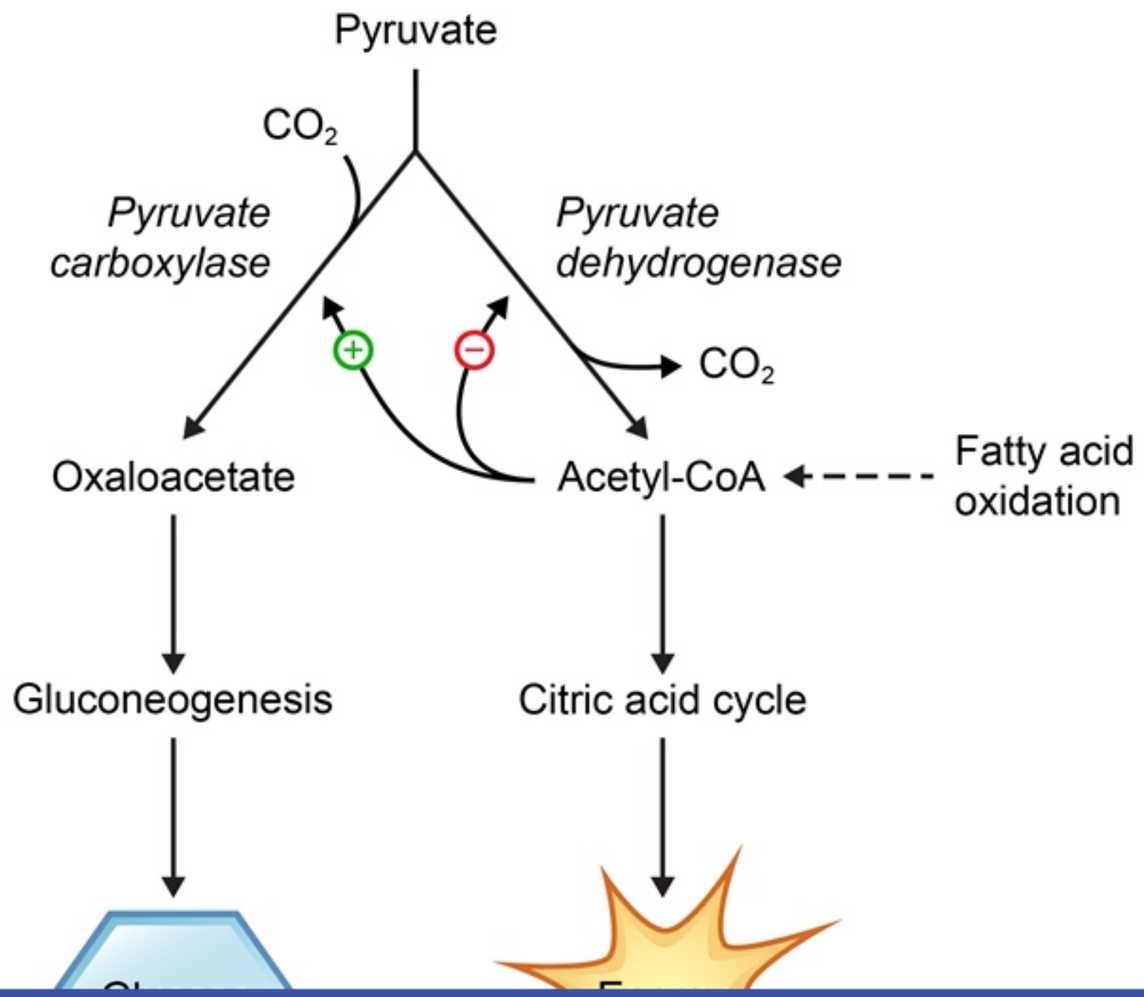
Metabolic fate of pyruvate



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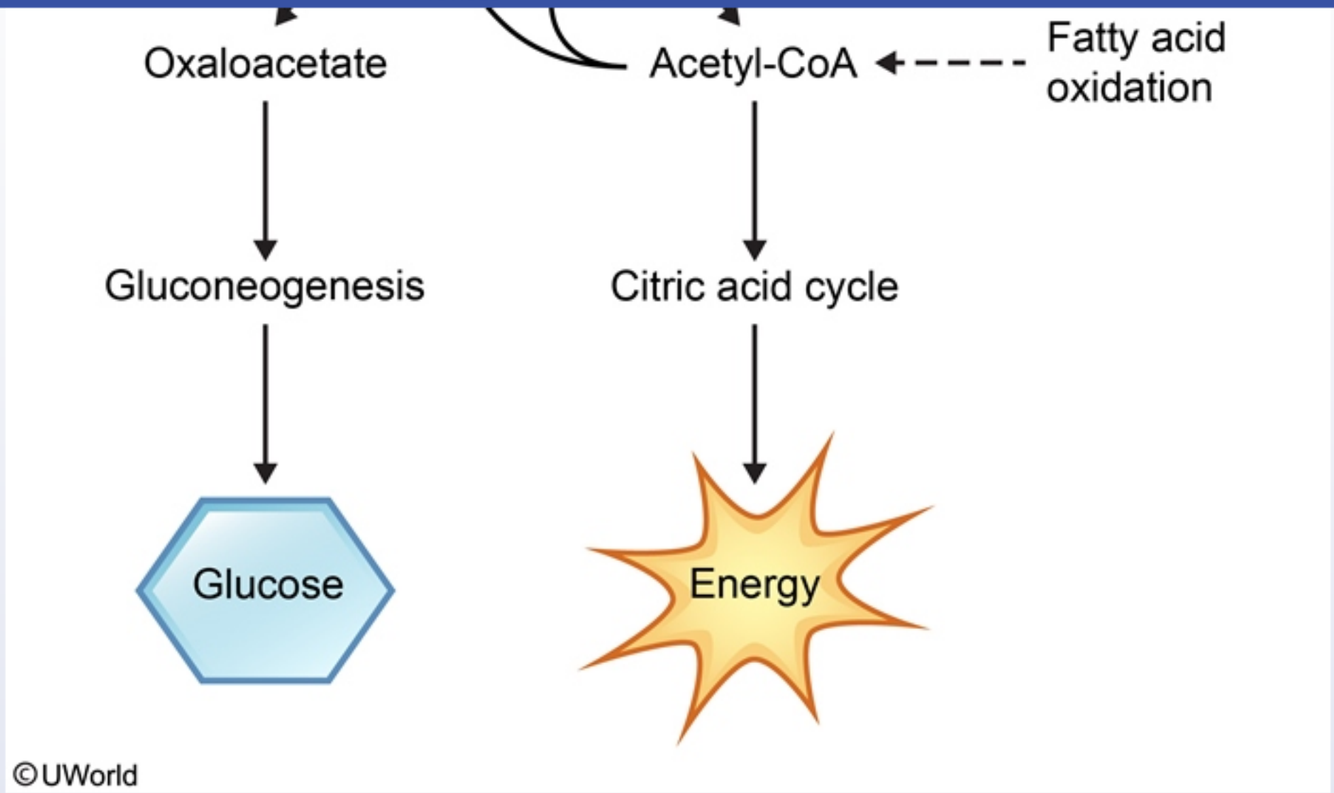

During gluconeogenesis, substances such as lactate and alanine are converted to pyruvate. However, pyruvate cannot be converted to phosphoenolpyruvate directly as pyruvate kinase is unidirectional. To convert pyruvate to phosphoenolpyruvate, pyruvate first undergoes biotin-dependent carboxylation to oxaloacetate in the mitochondria. This reaction is catalyzed by **pyruvate carboxylase**. The activity of pyruvate carboxylase is increased by **acetyl-CoA**. This critical regulatory step diverts pyruvate to pyruvate dehydrogenase when acetyl-CoA levels are too low, preventing the cell from becoming energy starved. When acetyl-CoA levels are high (as with increased beta oxidation of fatty acids during fasting), pyruvate carboxylase can operate at full capacity and convert most of the pyruvate into oxaloacetate for use in gluconeogenesis.

(Choice B) Muscle converts pyruvate to alanine via transamination, which is then transported to the liver where it is converted back to pyruvate for use in gluconeogenesis. Alanine allosterically inhibits pyruvate kinase, preventing phosphoenolpyruvate from being consumed by glycolysis

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(Choice C) Citrate is formed within mitochondria in the first reaction of the Krebs cycle, and elevated levels act as an indicator of high cellular energy stores and abundant biosynthetic intermediates. Citrate is therefore an important positive regulator of acetyl-CoA carboxylase and fructose-1,6-bisphosphatase, key enzymes involved in fatty acid synthesis and gluconeogenesis, respectively.

(Choice D) Regulation of glycolysis and gluconeogenesis occurs mainly through the inverse regulation of phosphofructokinase-1 and fructose 1,6-bisphosphatase by fructose 2,6-bisphosphate. High levels of fructose 2,6-bisphosphate activate phosphofructokinase-1 and accelerate glycolysis; low levels disinhibit fructose 1,6-bisphosphatase and promote gluconeogenesis.

(Choice E) Lactate is an important source of carbon atoms for glucose synthesis during gluconeogenesis. During anaerobic glycolysis in skeletal muscle, pyruvate is reduced to lactate by lactate dehydrogenase. Lactate formed in the contracting muscles is released into the bloodstream and transported to the liver, where it is converted back into glucose.

(Choice F) Oxaloacetate is the product of pyruvate carboxylase during gluconeogenesis. As such, increased levels of oxaloacetate would decrease the activity of the enzyme.

Educational objective:
Acetyl-CoA stimulates gluconeogenesis by increasing the activity of pyruvate carboxylase when acetyl-CoA is abundant. This regulatory step allows pyruvate to be shunted toward acetyl-CoA production when acetyl-CoA levels are low, preventing the cell from becoming depleted of

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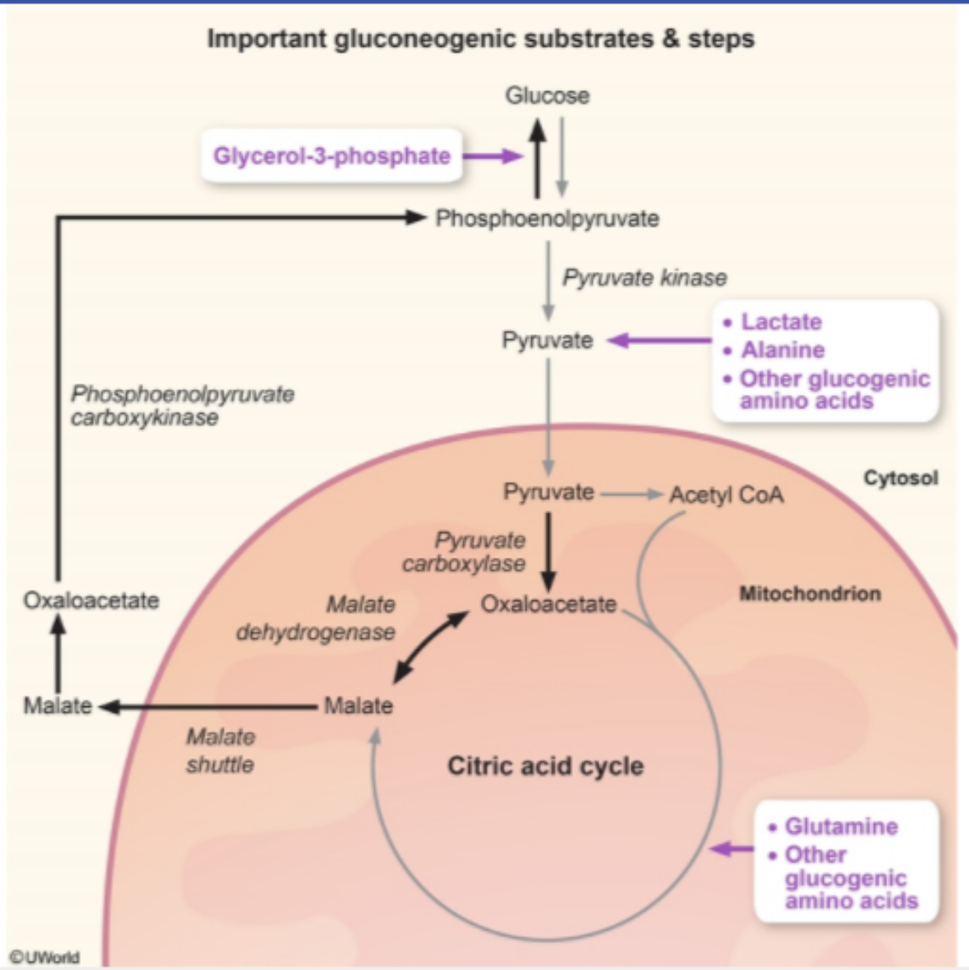

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allows pyruvate to be shunted toward acetyl CoA production when acetyl CoA levels are low, preventing the cell from becoming depleted of

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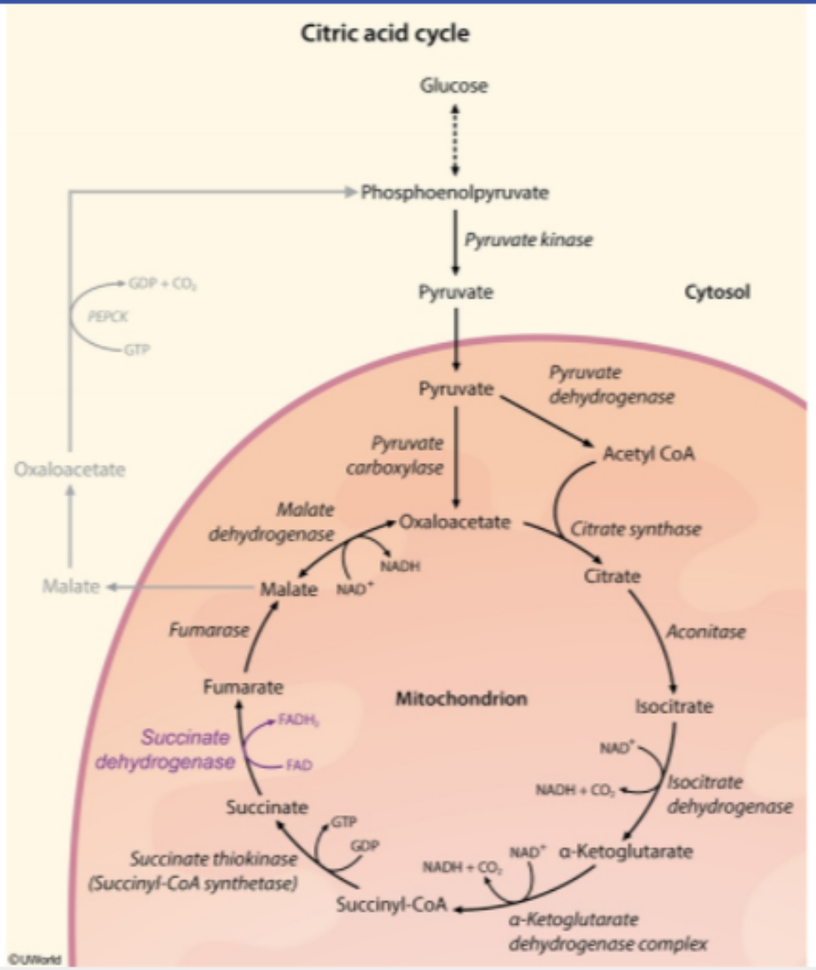

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References

- Regulation of the structure and activity of pyruvate carboxylase by acetyl CoA.
- Allosteric regulation of the biotin-dependent enzyme pyruvate carboxylase by acetyl-CoA.

Biochemistry	Endocrine, Diabetes & Metabolism	Gluconeogenesis
Subject	System	Topic

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Nutrition researchers investigating the relationship between fructose consumption and cardiovascular disease conduct a prospective cohort study on a population of randomly selected young adults. Study participants undergo semiannual measurement of waist circumference, blood pressure, and serum cholesterol and triglyceride concentrations. Dietary fructose consumption is assessed through the use of questionnaires and by measuring urinary fructose excretion. A 23-year-old man enrolled in the study is found to excrete large amounts of fructose in his urine compared to other study participants despite maintaining a moderate fructose intake. Further evaluation shows a hereditary defect in fructose metabolism, but he is asymptomatic and has no other medical problems. This patient most likely remains able to metabolize fructose due to the compensatory activity of which of the following enzymes?

A. Aldolase B
B. Aldose reductase
C. Fructokinase
D. Hexokinase
E. UDP-galactose-4-epimerase

Submit

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- A. Aldolase B (28%)
- B. Aldose reductase (15%)
- C. Fructokinase (21%)
- ✓ D. Hexokinase (30%)
- E. UDP-galactose-4-epimerase (4%)

Omitted
Correct answer
D

30%
Answered correctly

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Explanation

Disorders of fructose metabolism

Glucose

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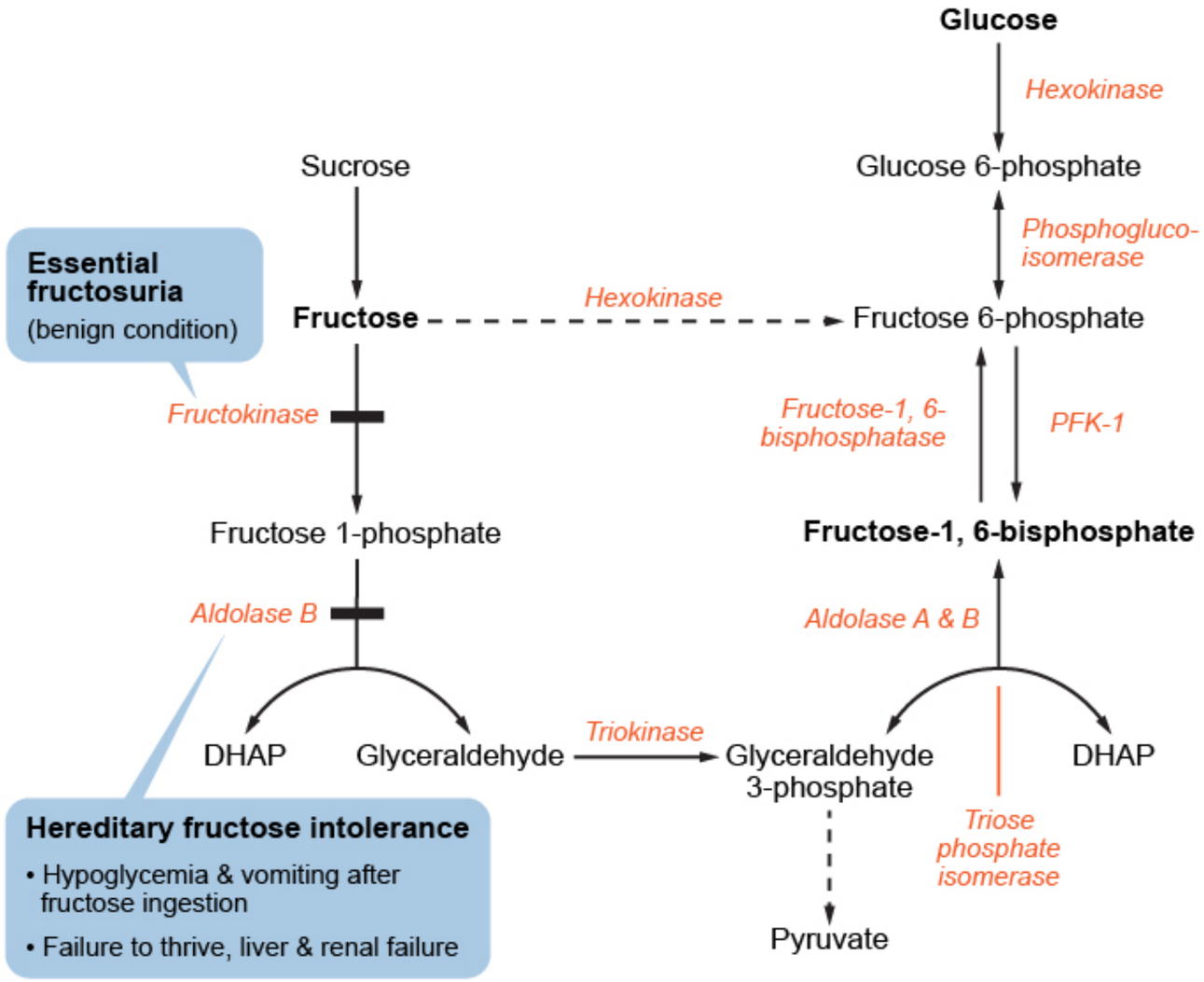
Disorders of fructose metabolism



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Fructose is obtained in the diet primarily from fruits and food sweeteners such as table sugar (sucrose) and high-fructose corn syrup. Fructose is absorbed in the proximal intestine through the GLUT5 fructose transporter. It is normally phosphorylated by **fructokinase** in the liver, yielding **fructose-1-phosphate**, which is converted by aldolase B to dihydroxyacetone phosphate (DHAP) and glyceraldehyde **(Choice C)**. Glyceraldehyde and DHAP can be converted to glyceraldehyde-3-phosphate, which can then be metabolized in the glycolytic pathway.

Fructokinase deficiency (essential fructosuria) is an **asymptomatic**, autosomal recessive disorder that causes dietary fructose to be excreted unchanged in the urine. In fructokinase deficiency, **hexokinase** takes over the role of fructose metabolism, converting dietary fructose into **fructose-6-phosphate**. Fructose-6-phosphate can be metabolized in the glycolytic pathway or converted to glucose-6-phosphate or glucose-1-phosphate, which can be used in the pentose phosphate pathway or for glycogen synthesis, respectively.

(Choice A) Aldolase B plays a nonessential role in glycolysis due to the redundant function of aldolase A. However, it is particularly important during fructose metabolism as deficiency of this enzyme leads to toxic accumulation of fructose-1-phosphate (hereditary fructose intolerance). This life-threatening disorder presents in infancy after the introduction of fructose-containing foods.

(Choice B) Aldose reductase is the enzyme that converts glucose to sorbitol. Aldose reductase has a low affinity for glucose, and normally only very small amounts of glucose are metabolized by this enzyme. The amount of glucose metabolized by the aldose reductase pathway increases significantly in diabetes mellitus and contributes to chronic complications such as neuropathy and retinopathy.

(Choice E) UDP-galactose-4-epimerase is involved in the metabolism of galactose; it does not play a role in fructose metabolism.

Educational objective:
Essential fructosuria is a benign disorder of fructose metabolism caused by fructokinase deficiency. In patients with essential fructosuria, some of the dietary fructose load is converted by hexokinase to fructose-6-phosphate, which can then enter glycolysis; this pathway is not significant in normal individuals.

Biochemistry	Endocrine, Diabetes & Metabolism	Fructose metabolism
Subject	System	Topic

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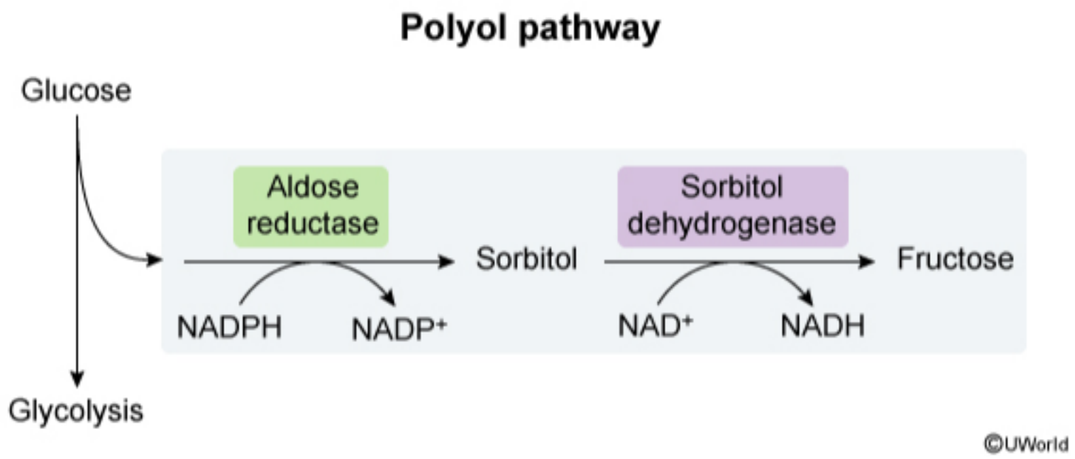

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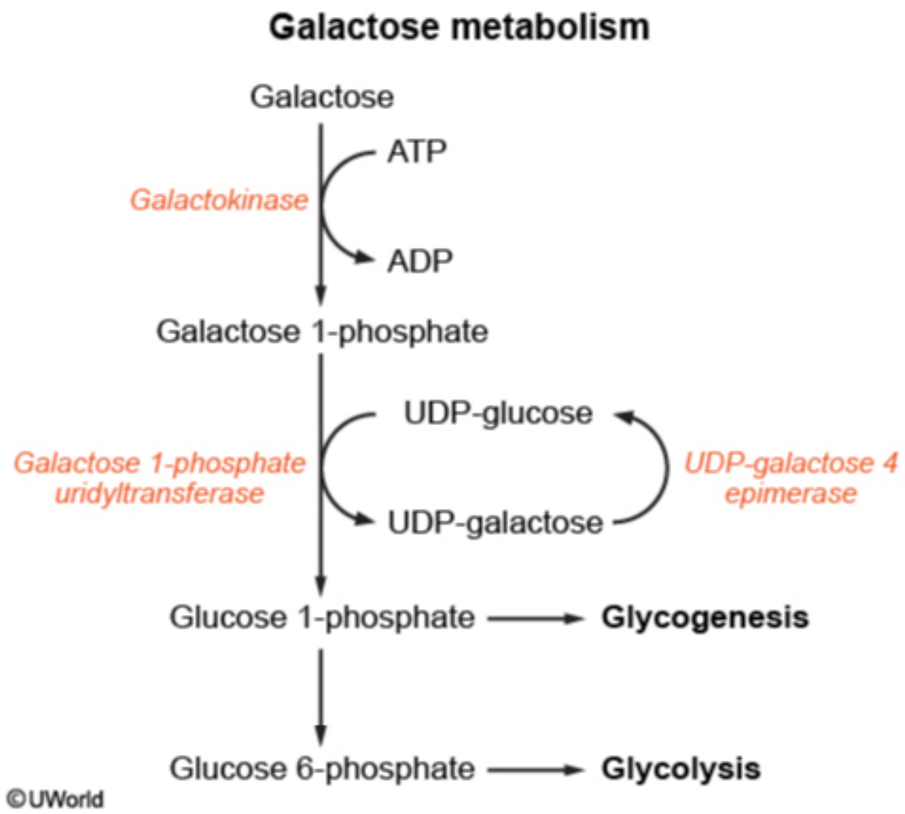

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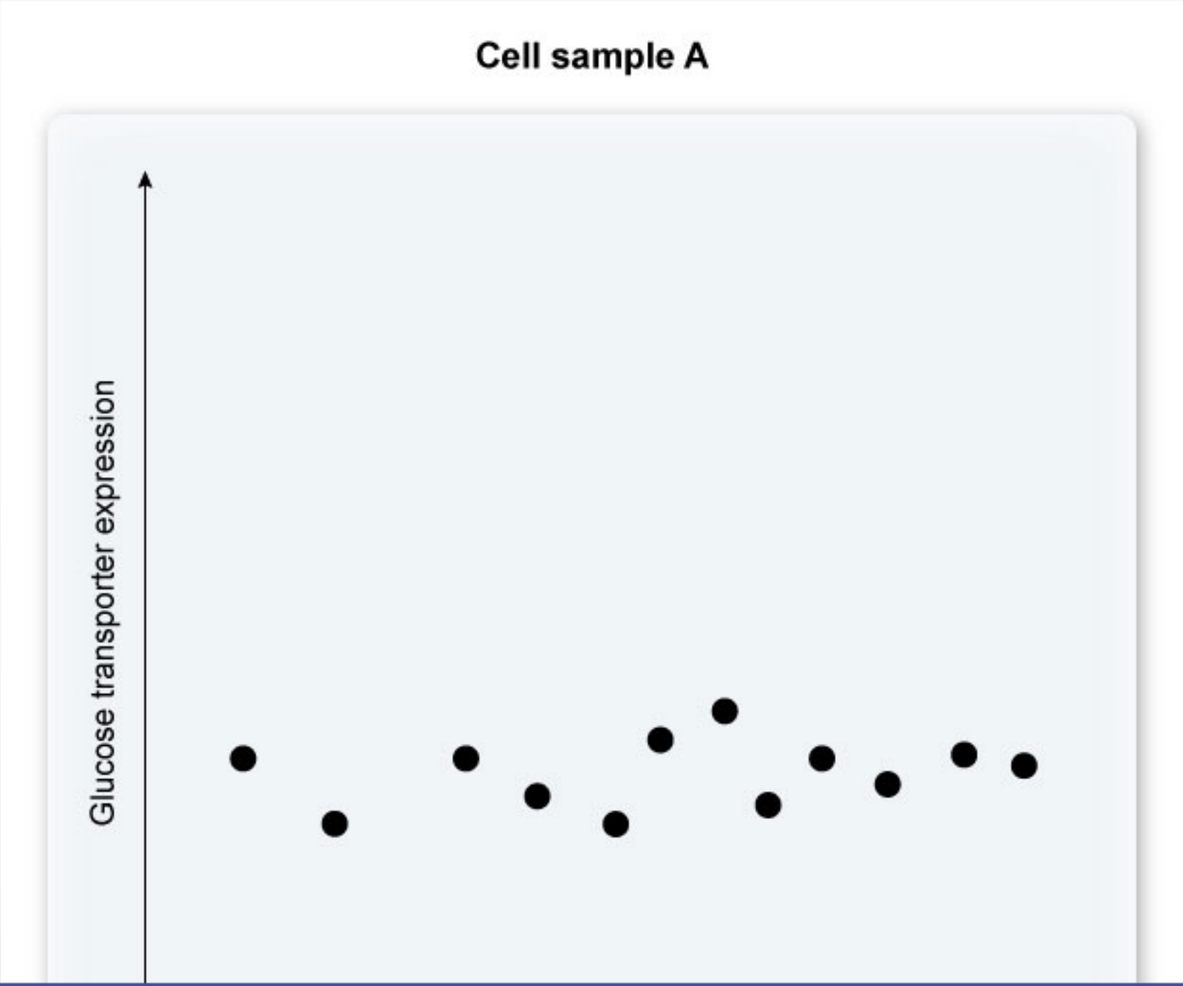
Researchers are investigating the relationship between glucose transport proteins and insulin concentration in different types of tissues. Experiments in which cells are taken from various tissue samples and exposed to increasing concentrations of insulin are performed. The number of surface glucose transporters are then measured. The results from 2 cell samples are plotted on the graphs below.



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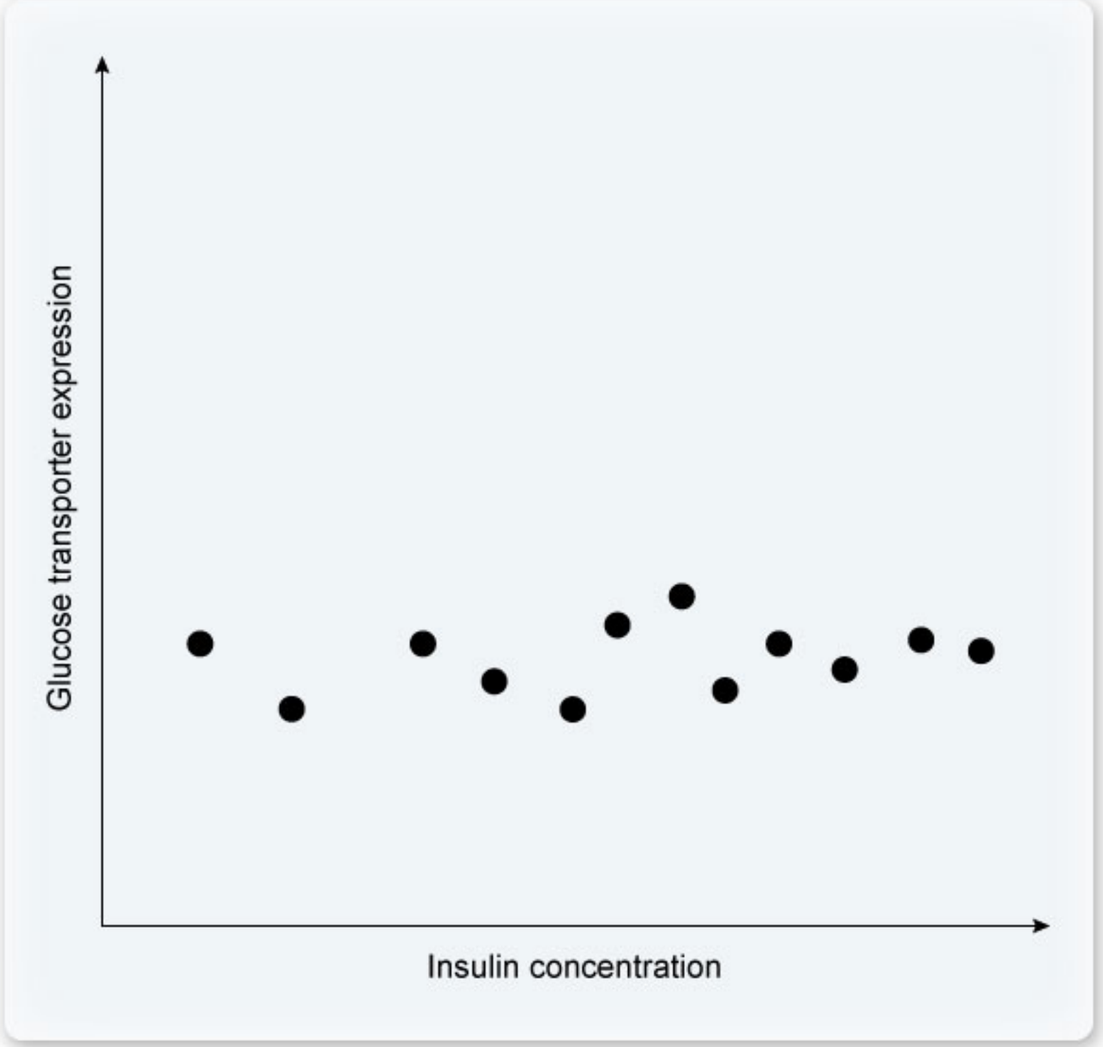

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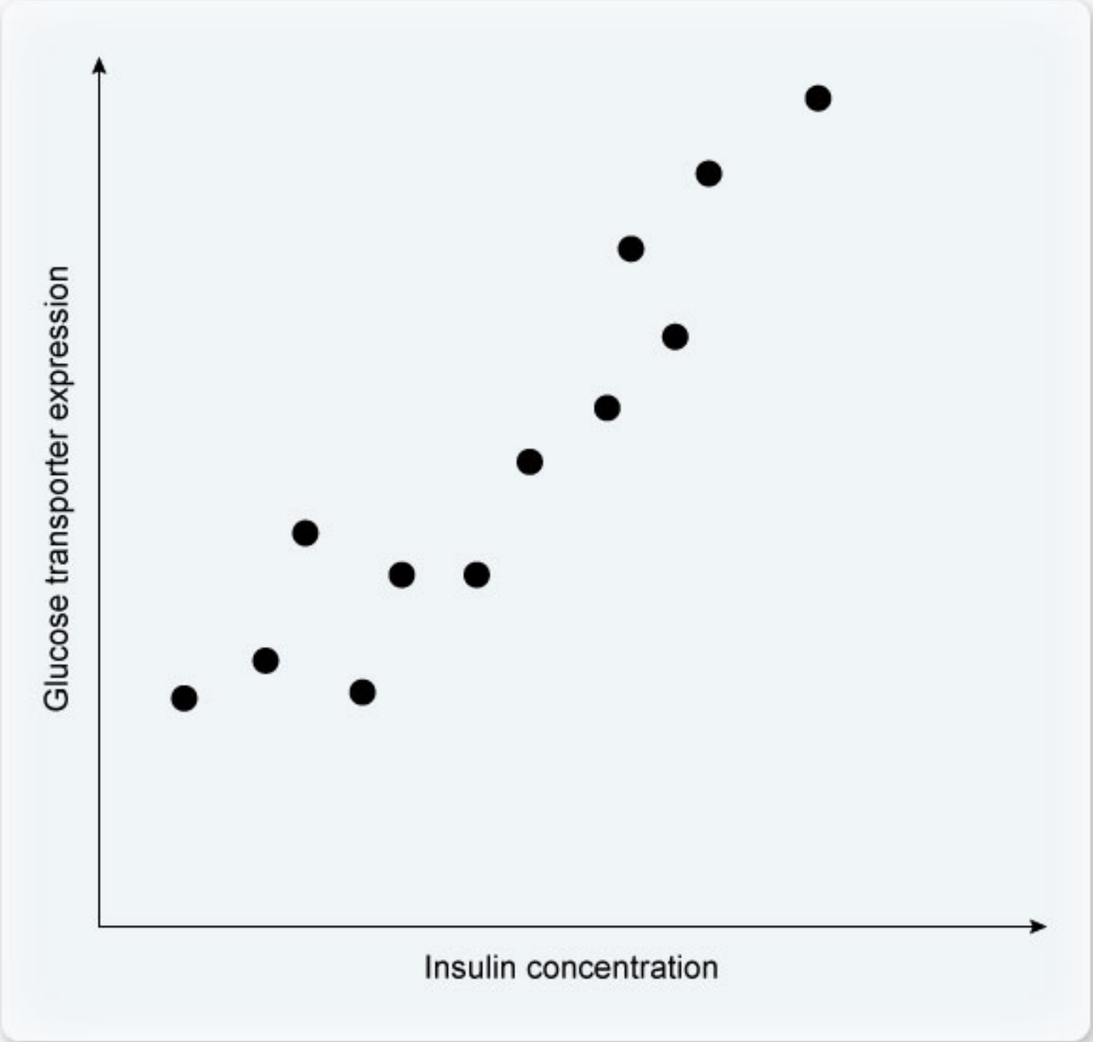
Cell sample B



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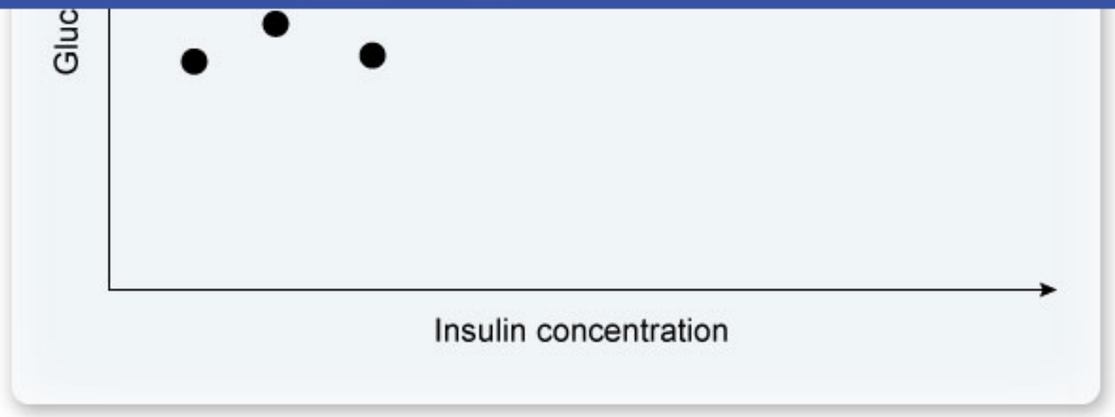

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Which of the following cell types are most likely represented in cell samples A and B, respectively?

	Cell sample A	Cell sample B
A.	Cerebral neurons	Hepatocytes
B.	Intestinal epithelial cells	Pancreatic beta cells
C.	Renal tubular cells	Hepatocytes
D.	Renal tubular cells	Skeletal myocytes
E.	Skeletal myocytes	Adipocytes

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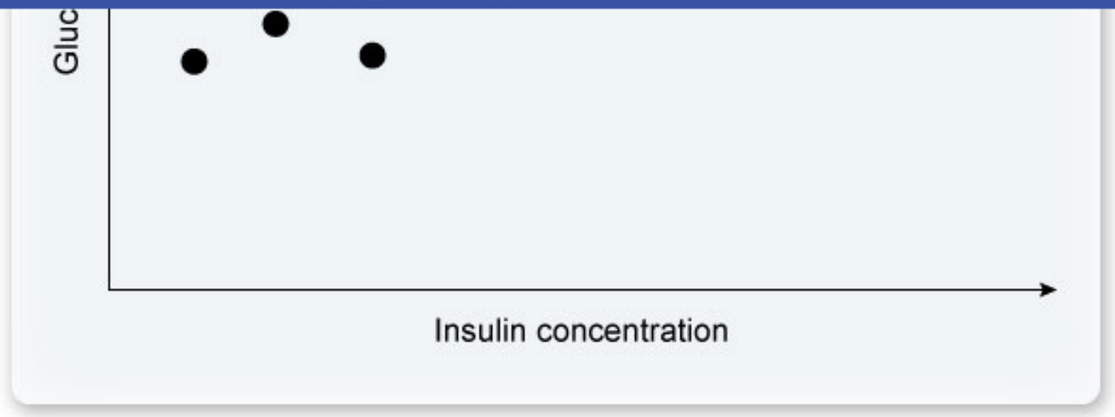

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Which of the following cell types are most likely represented in cell samples A and B, respectively?

	Cell sample A	Cell sample B
A.	Cerebral neurons (24%)	Hepatocytes
B.	Intestinal epithelial cells (5%)	Pancreatic beta cells
C.	Renal tubular cells (9%)	Hepatocytes
✓ D.	Renal tubular cells (54%)	Skeletal myocytes
E.	Skeletal myocytes (6%)	Adipocytes

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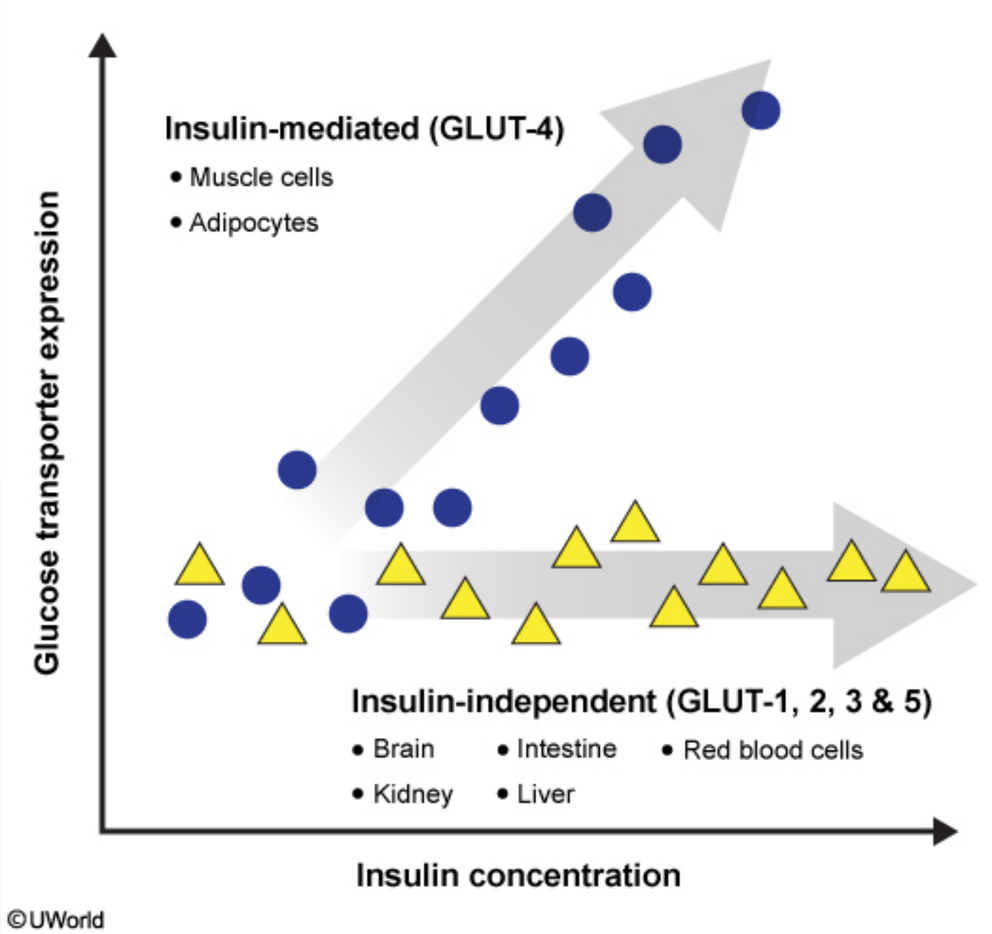

The **glucose transport proteins** (GLUTs) are a family of transmembrane proteins responsible for transport of glucose across cell membranes. Of these, only **GLUT-4** is **responsive to insulin**. In the absence of insulin, GLUT-4 is sequestered in the cytoplasm and the cells become less permeable to glucose. However, increasing insulin concentrations induce translocation of GLUT-4 to the plasma membrane, facilitating glucose transport into the cell (**sample B**). GLUT-4 is predominantly expressed in **skeletal muscle cells and adipocytes**, where it facilitates insulin-

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In contrast to GLUT-4, **GLUTs 1, 2, 3, and 5** are always present on the plasma membrane, regardless of insulin levels, and are responsible for **insulin-independent** glucose transport (**sample A**).

- GLUT-1 contributes to basal glucose transport in erythrocytes and at the blood-brain barrier.
- GLUT-2 is present in hepatocytes, pancreatic beta cells, and at the basolateral membrane of **renal tubules** and small intestinal mucosa. It plays a role in absorption of dietary glucose, reabsorption of glucose from renal tubules, hepatic glucose regulation, and sensitivity of beta cells to circulating glucose.
- GLUT-3 is involved in placental and neuronal glucose transport.
- GLUT-5 is a fructose transporter found in spermatocytes and the gastrointestinal tract.

(Choices A, B, and C) Glucose uptake by hepatocytes, pancreatic beta cells, neurons, and enterocytes primarily involves insulin-independent glucose transporters and does not substantially change with insulin concentration.

(Choice E) Both skeletal myocytes and adipocytes express GLUT-4 and would show increased glucose uptake in response to insulin.

Educational objective:
Glucose transport protein (GLUT)-4 is an insulin-sensitive glucose transporter expressed in skeletal muscle cells and adipocytes that translocates to the plasma membrane in response to increasing insulin levels. In contrast, GLUT-1, 2, 3, and 5 are always present on the plasma membrane and constitutively transport glucose in an insulin-independent manner.

References

- Cellular regulation of glucose uptake by glucose transporter GLUT4.

Biochemistry Endocrine, Diabetes & Metabolism Diabetes mellitus

A 4-day-old infant is brought to the emergency department with abnormal movements. The patient has had intermittent episodes of tonic posturing over the past 3 hours as well as poor feeding, vomiting, and irritability for the past 2 days. The mother also reports that his diapers smell like "caramelizing sugar." There are no known medical problems in the family, but the child's maternal aunt died "sometime in the first year" of life from unknown causes. Examination shows a lethargic infant with intermittent posturing episodes and increased generalized muscle tone. Laboratory studies of plasma and urine confirm the diagnosis. In addition to appropriate dietary restriction, supplementation with which of the following may improve this infant's condition?

A. Arginine

B. Cobalamin

C. Pyridoxine

D. Tetrahydrobiopterin

E. Thiamine

Submit

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A. Arginine (15%)

B. Cobalamin (5%)

C. Pyridoxine (18%)

D. Tetrahydrobiopterin (19%)

✓ E. Thiamine (41%)

Omitted
Correct answer
E

41%
Answered correctly

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Time Spent

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Last Updated

Explanation

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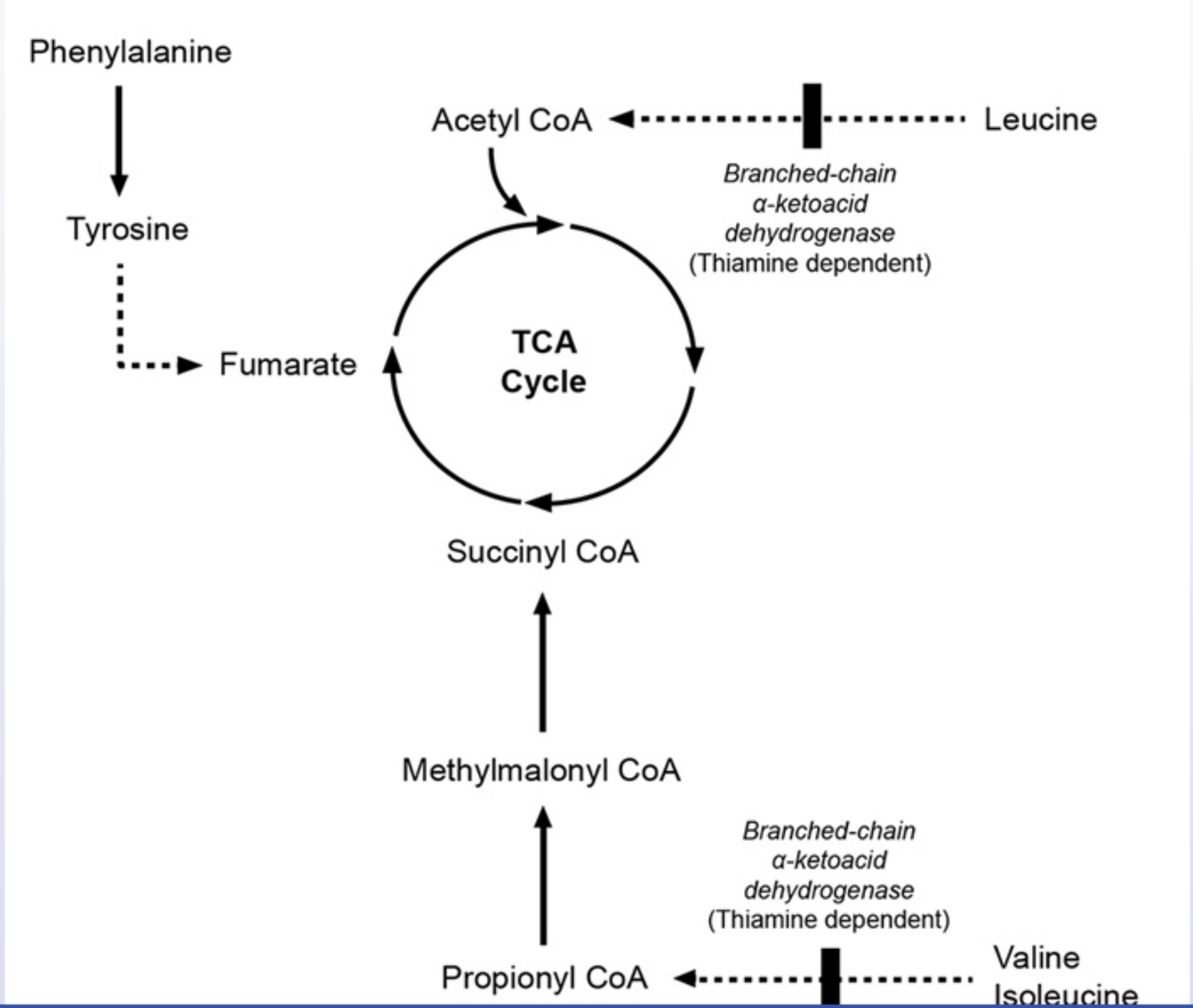

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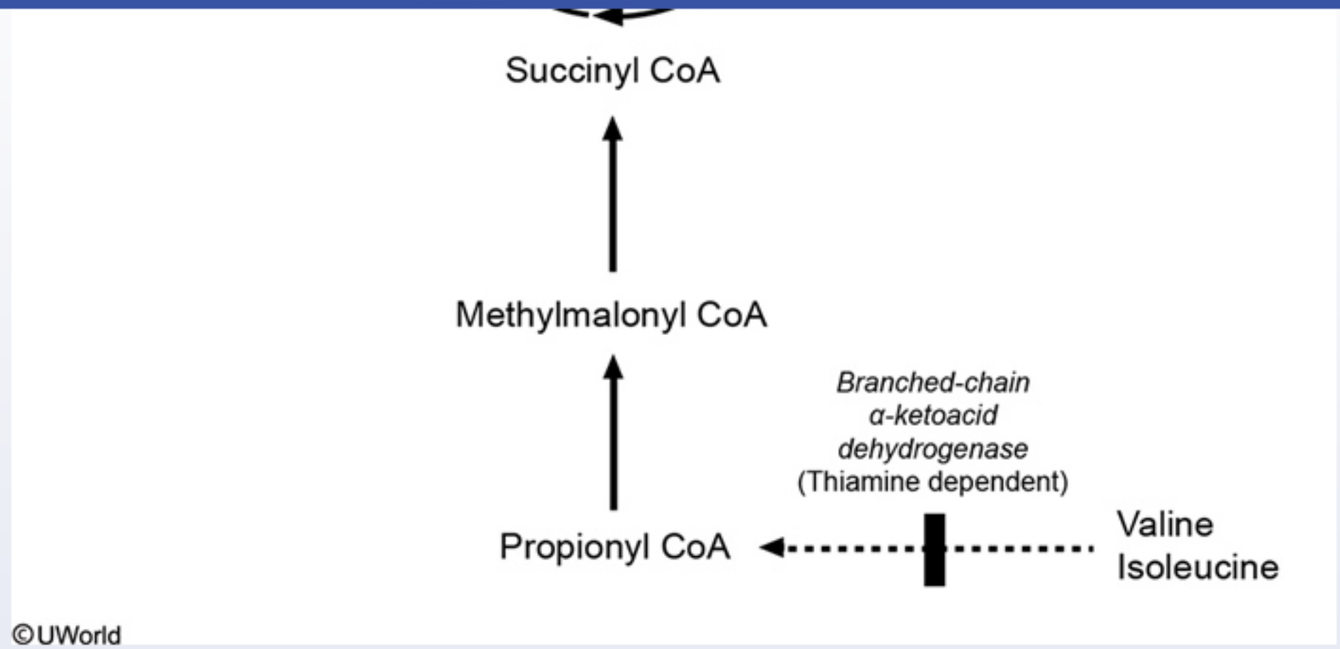

This infant has symptoms typical of **maple syrup urine disease (MSUD)**, an autosomal recessive disorder characterized by the defective breakdown of branched-chain amino acids (**leucine**, **isoleucine**, and **valine**). Degradation of these 3 amino acids first involves transamination to their respective α-ketoacids, which are subsequently metabolized by several enzymes referred to as the **branched-chain α-ketoacid dehydrogenase complex** (BCKDC).

Mutations in BCKDC result in accumulation of the branched-chain amino acids in serum and peripheral tissues, resulting in **neurotoxicity** that includes seizures, irritability, lethargy, and poor feeding. A metabolite of isoleucine gives the urine a distinctive **sweet odor**. MSUD can be life-threatening if untreated, as brain swelling may lead to death.

Branched-chain α-ketoacid dehydrogenase (in addition to pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) requires 5 cofactors: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with MSUD improve with high-dose **thiamine treatment**, but most still require lifelong dietary restrictions.

(Choice A) Most disorders of the urea cycle require arginine as an essential amino acid. When patients with urea cycle disorders develop

This infant has symptoms typical of **maple syrup urine disease (MSUD)**, an autosomal recessive disorder characterized by the defective breakdown of branched-chain amino acids (**leucine**, **isoleucine**, and **valine**). Degradation of these 3 amino acids first involves transamination to their respective α-ketoacids, which are subsequently metabolized by several enzymes referred to as the **branched-chain α-ketoacid dehydrogenase complex** (BCKDC).

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(Choice A) Most disorders of the urea cycle require arginine as an essential amino acid. When patients with urea cycle disorders develop hyperammonemia, arginine is administered for production of downstream water-soluble intermediates (eg, ornithine, citrulline) that lead to nitrogen disposal and decreased plasma ammonia levels.

(Choice B) Cobalamin (vitamin B_{12}) deficiency leads to megaloblastic anemia, neurologic changes including peripheral neuropathy, and elevated plasma levels of homocysteine (a prothrombotic substance). Supplementation of cobalamin is recommended to lower homocysteine levels in patients with hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism, as well as heme and neurotransmitter synthesis. Pyridoxine supplementation is also used in the treatment of hyperhomocysteinemia.

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria, as tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:
Branched-chain α-ketoacid dehydrogenase requires several coenzymes: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with maple syrup urine disease improve with high-dose thiamine treatment, but most require lifelong restriction of leucine, isoleucine, and valine.

Thiamine, Lipoate, Coenzyme A, FAD, NAD (mnemonic: Tender Loving Care For Nancy). Some patients with MSUD improve with high-dose **thiamine treatment**, but most still require lifelong dietary restrictions.

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Branched-chain α-ketoacid dehydrogenase requires several coenzymes: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with maple syrup urine disease improve with high-dose thiamine treatment, but most require lifelong restriction of leucine, isoleucine, and valine.

References

- Branched-chain amino acid metabolism: From rare Mendelian diseases to more common disorders.
- Maple syrup urine disease.

Biochemistry	Endocrine, Diabetes & Metabolism	Maple syrup urine disease
Subject	System	Topic

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A 14-year-old boy is brought to the emergency department due to excessive urination and thirst. He has lost 4.5 kg (10 lb) in the last 3 weeks. The patient has no past medical problems. His father has type 1 diabetes mellitus. Physical examination shows dry mucous membranes. Laboratory studies reveal blood glucose of 455 mg/dL, normal anion gap, and hemoglobin A1c of 11.3%. The patient is diagnosed with type 1 diabetes, and treatment with insulin is initiated. In addition to lowering blood glucose, insulin increases glycogen synthesis in hepatocytes. Activation of which of the following molecules most likely promotes this metabolic effect?

- A. Janus kinase (JAK)
- B. Lipoxygenase
- C. Phospholipase C
- D. Protein kinase A
- E. Protein phosphatase

Submit

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- A. Janus kinase (JAK) (23%)
- B. Lipoxygenase (1%)
- C. Phospholipase C (9%)
- D. Protein kinase A (27%)
- ✓ E. Protein phosphatase (38%)

Omitted
Correct answer
E

38%
Answered correctly

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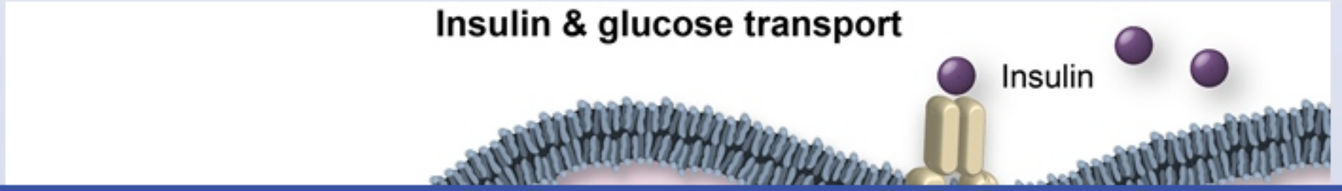
Last Updated

Explanation



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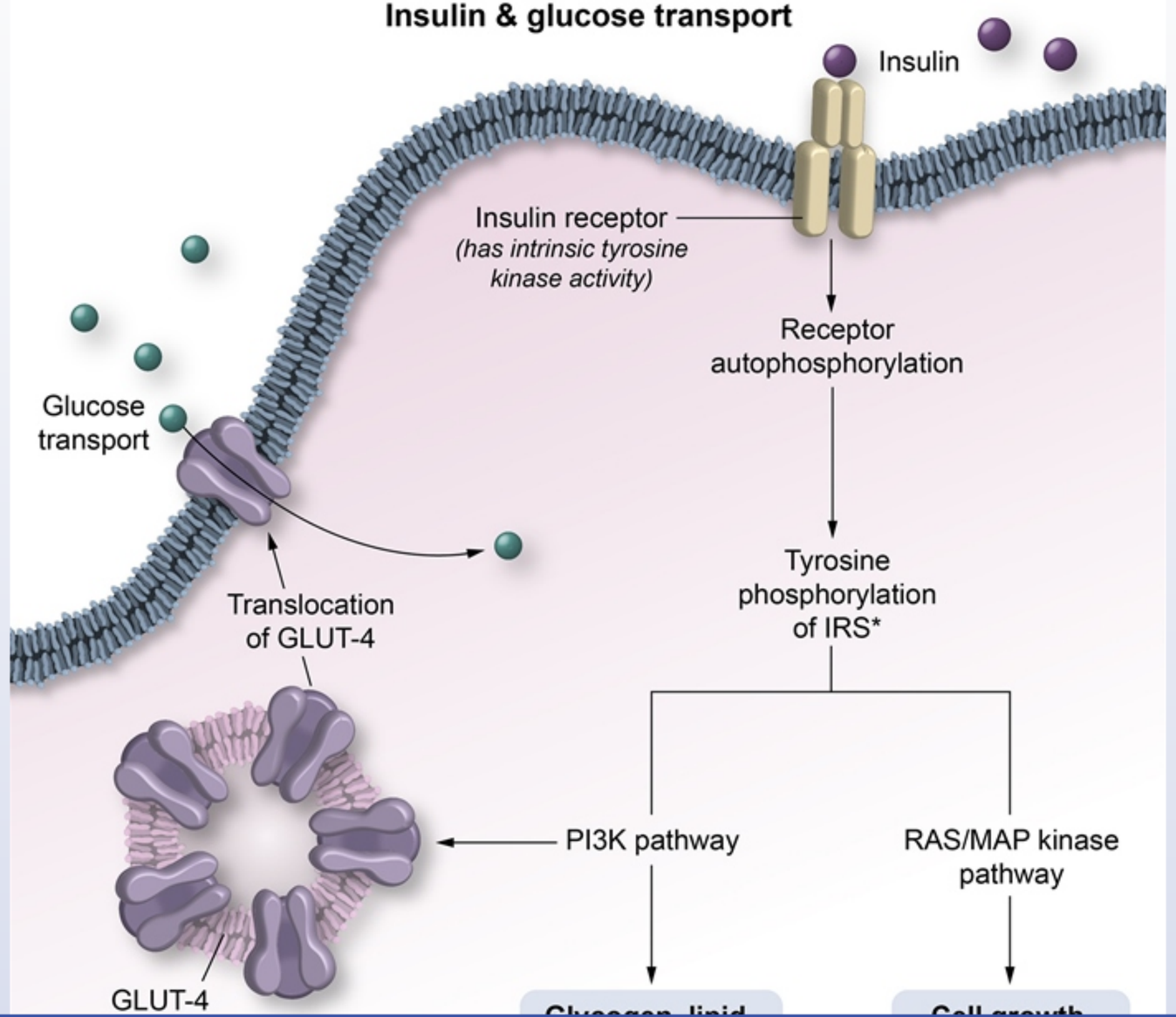
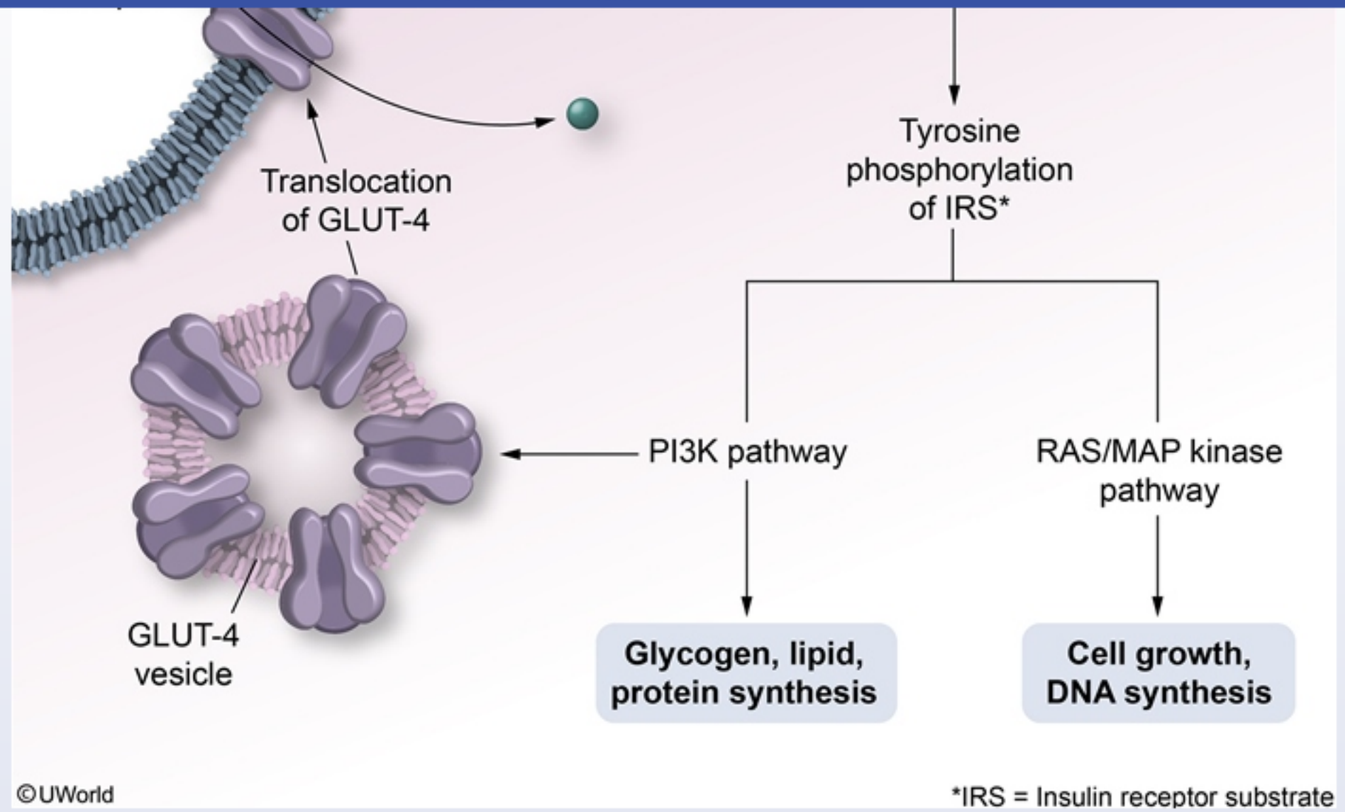
Insulin & glucose transport





Insulin decreases blood glucose levels by increasing glucose uptake into skeletal muscle and adipocytes. In addition to having glucose lowering effects, insulin is an anabolic hormone that promotes synthesis of glycogen, triglycerides, nucleic acids, and proteins. Furthermore, insulin inhibits glycogenolysis and gluconeogenesis.

The surface receptor for insulin is a transmembrane protein with **intrinsic tyrosine kinase** activity in its cytoplasmic domain. Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 then activates several intracellular pathways that induce the physiologic effects of insulin. Activation of the MAP kinase pathway promotes mitogenic functions such as DNA synthesis and cell growth. In contrast, activation of **phosphatidylinositol-3-kinase (PI3K)** stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, **glycogen synthesis**, and fat synthesis. PI3K promotes glycogen synthesis by activating **protein phosphatase**, an enzyme that

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(Choice A) Janus kinase (JAK) is a component of the second messenger system for various peptide hormones (eg, growth hormone, prolactin) and cytokines (eg, interferon, interleukin). JAK has tyrosine kinase activity; however, it is a cytoplasmic enzyme that is not part of a cell surface receptor (non-receptor tyrosine kinase).

(Choice B) Lipoxygenase is an enzyme involved in arachidonic acid metabolism and is responsible for the arm of that pathway that synthesizes leukotrienes.

(Choice C) Phospholipase C is activated in the G-protein/inositol triphosphate (IP_3)/calcium second messenger system. Hormone-receptor binding activates a G-protein that in turn activates phospholipase C to degrade phospholipids into IP_3 and diacylglycerol. Both diacylglycerol and the increased intracellular calcium caused by IP_3 lead to protein kinase C activation.

(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:
Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and nucleic acids. Tyrosine kinase/phosphatidylinositol-3-kinase stimulation promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates (activates) glycogen synthase.

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Educational objective:
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References

- Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions.

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Educational objective:
Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and nucleic acids. Tyrosine kinase/phosphatidylinositol-3-kinase stimulation promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates (activates) glycogen synthase.

References

- Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions.

Biochemistry	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

An 18-year-old girl with a history of type 1 diabetes mellitus comes to the emergency department after several hours of nausea, vomiting, and abdominal pain. The patient reports that she is on vacation visiting friends and has not taken insulin in the last 2 days. Physical examination shows breath with fruity odor and dry mucosal membranes. Laboratory studies show a blood glucose level of 452 mg/dL and high anion gap metabolic acidosis. Urinalysis is positive for ketones. It is determined that the patient's insulin deficiency is causing increased production of gluconeogenic precursors that are subsequently converted to glucose in the liver. Which of the following enzymes is most likely to provide these precursor substrates?

A. Acetyl CoA carboxylase

B. Acyl CoA synthetase

C. ATP citrate lyase

D. Glucose-6-phosphate dehydrogenase

E. Glycerol kinase

Submit

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- A. Acetyl CoA carboxylase (41%)
- B. Acyl CoA synthetase (25%)
- C. ATP citrate lyase (4%)
- D. Glucose-6-phosphate dehydrogenase (8%)
- ✓ E. Glycerol kinase (19%)

Omitted
Correct answer
E

19%
Answered correctly

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Explanation

Triglyceride metabolism

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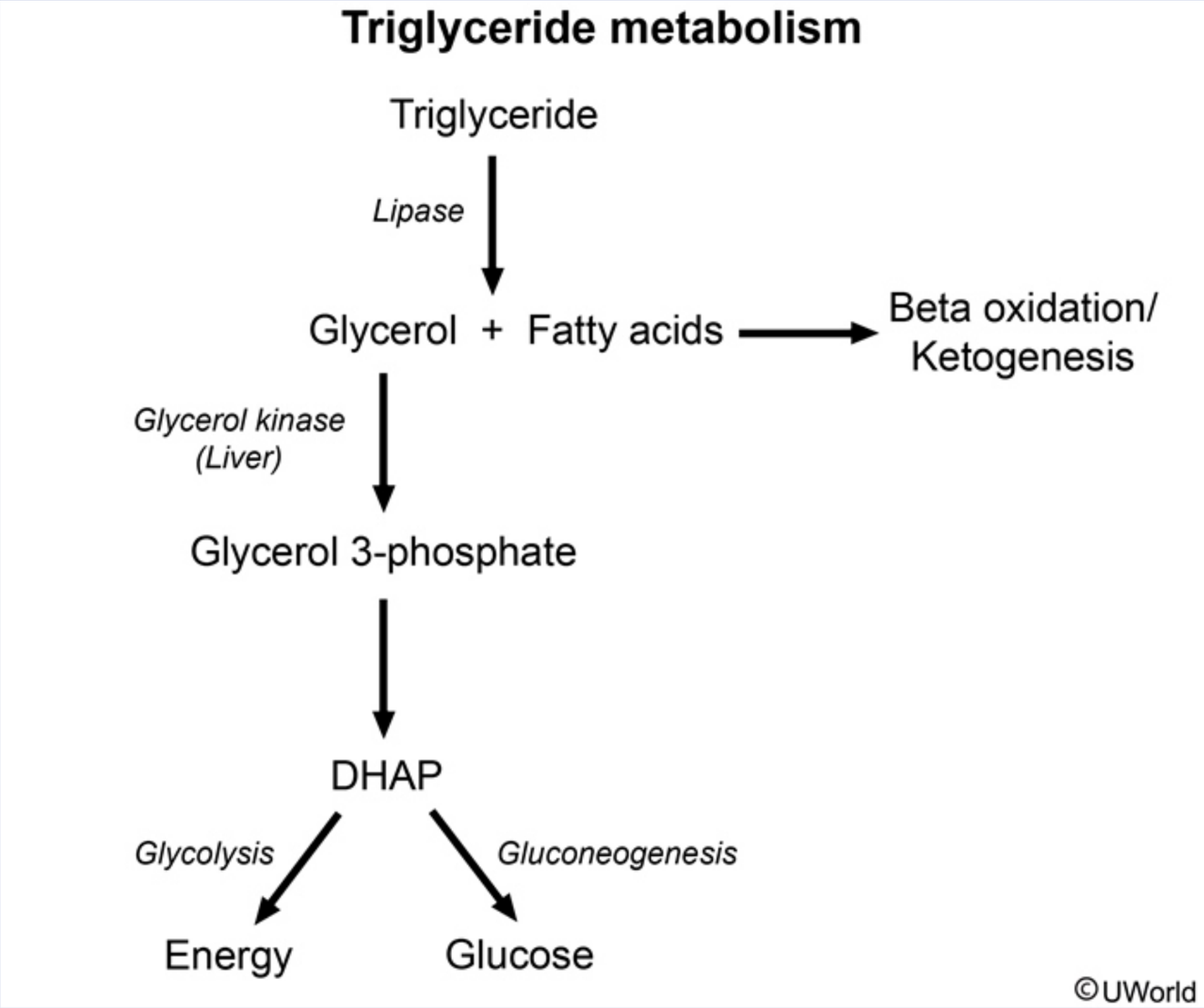

This patient in **diabetic ketoacidosis** is experiencing increased triglyceride breakdown in adipose tissue due to her insulin deficiency.

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This patient in **diabetic ketoacidosis** is experiencing increased triglyceride breakdown in adipose tissue due to her insulin deficiency. Triglycerides stored in adipose tissue are metabolized to free fatty acids and **glycerol** by hormone-sensitive lipase in response to low insulin and high catecholamine levels. Adipocytes are unable to metabolize glycerol, so it is secreted into the circulation and transported to the liver, where it is phosphorylated to glycerol-3-phosphate by **glycerol kinase**. Glycerol-3-phosphate is subsequently converted by glycerol-3-phosphate dehydrogenase to dihydroxyacetone phosphate (DHAP), which can be used to produce **glucose** through **gluconeogenesis**.

(Choice A) Acetyl CoA carboxylase is a biotin-dependent enzyme present in both liver and adipose tissues. It catalyzes the first committed step in fatty acid synthesis, the conversion of acetyl CoA to malonyl CoA.

(Choice B) Fatty acids must first be activated by acyl CoA synthetase in the cytoplasm in order to undergo beta-oxidation in mitochondria. Although beta-oxidation of fatty acids is increased in diabetic ketoacidosis, the resulting acetyl-CoA is used for energy and ketone body formation (not glucose production).

(Choice C) In contrast to fatty acid oxidation, which occurs in mitochondria, fatty acid synthesis occurs in the cytosol. Acetyl CoA generated in mitochondria during glycolysis is transferred to the cytosol as citrate. In the cytoplasm, ATP citrate lyase converts citrate back into acetyl CoA that can be used for fatty acid chain elongation.

(Choice D) Glucose-6-phosphate dehydrogenase is the first enzyme of the hexose monophosphate (HMP) shunt. The HMP shunt produces pentose sugars for nucleotide synthesis and NADPH, which is necessary for cholesterol and fatty acid biosynthesis.

Educational objective:
Glycerol produced by the degradation of triglycerides in adipose tissue can be used by glycerol kinase in the liver and kidney to synthesize glucose during gluconeogenesis.

Biochemistry	Endocrine, Diabetes & Metabolism	Triglyceride metabolism
Subject	System	Topic

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A young Ashkenazi Jewish couple comes to the obstetrician with interest in conceiving a child. They are offered genetic screening due to the high rate of rare disease carriers in this population. Pre-conception genetic test results show that both are carriers for an autosomal recessive disorder of sphingomyelinase deficiency. They are counseled about the 1 in 4 chance that their offspring will be affected by this disorder. The couple wants to know the clinical features of an affected child. Which of the following is most consistent with this condition?

A. Bone pain and pancytopenia

B. Dysostosis multiplex and corneal clouding

C. Neurodegeneration and hepatosplenomegaly

D. Neuropathic pain and angiokeratomas

E. Small stature and infertility

Submit

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- A. Bone pain and pancytopenia (1%)
- B. Dysostosis multiplex and corneal clouding (4%)
- ✓ C. Neurodegeneration and hepatosplenomegaly (87%)
- D. Neuropathic pain and angiokeratomas (4%)
- E. Small stature and infertility (1%)

Omitted
Correct answer
C

87%
Answered correctly

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Time Spent

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Last Updated

Explanation

Sphingolipidoses				
Diagnosis	Inheritance	Deficiency	Accumulated substrate	Key features

Sphingolipidoses				
Diagnosis	**Inheritance**	**Deficiency**	**Accumulated substrate**	**Key features**
Fabry	XLR	α-galactosidase	Globotriaosylceramide	• Angiokeratomas • Peripheral neuropathy • Glomerulopathy
Tay-Sachs	AR	β-hexosaminidase A	GM2 (ganglioside)	• Macular cherry-red spot • Progressive neurodegeneration
Gaucher		β-glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia
Niemann-Pick		Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
				• Progressive

Gaucher	AR	β-glucocerebrosidase	Glucocerebroside	• Hepatosplenomegaly • Pancytopenia • Bone pain/osteopenia
Niemann-Pick		Sphingomyelinase	Sphingomyelin	• Macular cherry-red spot • Progressive neurodegeneration • Hepatosplenomegaly
Krabbe		Galactocerebrosidase	Galactocerebroside & psychosine	• Progressive neurodegeneration • Peripheral neuropathy • Optic atrophy
Metachromatic leukodystrophy		Arylsulfatase A	Cerebroside sulfate	• Progressive neurodegeneration • Peripheral neuropathy

AR = autosomal recessive; **XLR** = X-linked recessive.

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Niemann-Pick disease is an **autosomal recessive** lipid storage disorder caused by **sphingomyelinase deficiency**. Sphingomyelinase is the enzyme responsible for sphingomyelin metabolism, and the excess sphingomyelin results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells (black arrows) accumulate in the liver and spleen (**hepatosplenomegaly**) and central nervous system (**hypotonia, neurodegeneration**). Following a period of normal development, infants fail to attain new skills and lose previously acquired milestones (eg, sitting with support, head control, social smile). Retinal accumulation leads to a cherry-red macular spot (blue arrow). Death usually occurs by age 3.

Niemann-Pick disease and other rare genetic disorders (eg, Tay-Sachs disease, Gaucher disease, Bloom syndrome) are more common among the **Ashkenazi Jewish** population. The increased risk of rare and often life-threatening genetic mutations is attributed to the "**founder effect**," which refers to the loss of genetic variability within a group that historically conceived within their own community. Prior to conceiving a child, an

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(Choice A) Gaucher disease, the most common genetic disorder among Ashkenazi Jews, is characterized by β-glucocerebrosidase deficiency and glucocerebroside accumulation. Typical features include hepatosplenomegaly, pancytopenia, and severe bone pain.

(Choice B) Hurler syndrome is a mucopolysaccharidosis that leads to dysostosis multiplex (eg, enlarged skull, abnormally shaped ribs and vertebrae) and corneal clouding, which can cause blindness. This disorder is characterized by accumulation of heparan sulfate and dermatan sulfate due to α-L-iduronidase deficiency.

(Choice D) In Fabry disease, α-galactosidase A deficiency causes globotriaosylceramide (ceramide trihexoside) accumulation. Disease manifestations include neuropathic pain and angiokeratomas in adolescence and multi-organ involvement (renal, cerebrovascular, cardiac) in adulthood.

(Choice E) Small stature and infertility along with a predisposition to malignancy and a classic sun-sensitive facial rash are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability.

Educational objective:
Niemann-Pick disease is an autosomal recessive disorder that is common in the Ashkenazi Jewish population. This disorder is characterized by sphingomyelinase deficiency and sphingomyelin accumulation, which cause hepatosplenomegaly and neurologic regression in infancy.

References

Niemann-Pick disease is an **autosomal recessive** lipid storage disorder caused by **sphingomyelinase deficiency**. Sphingomyelinase is the

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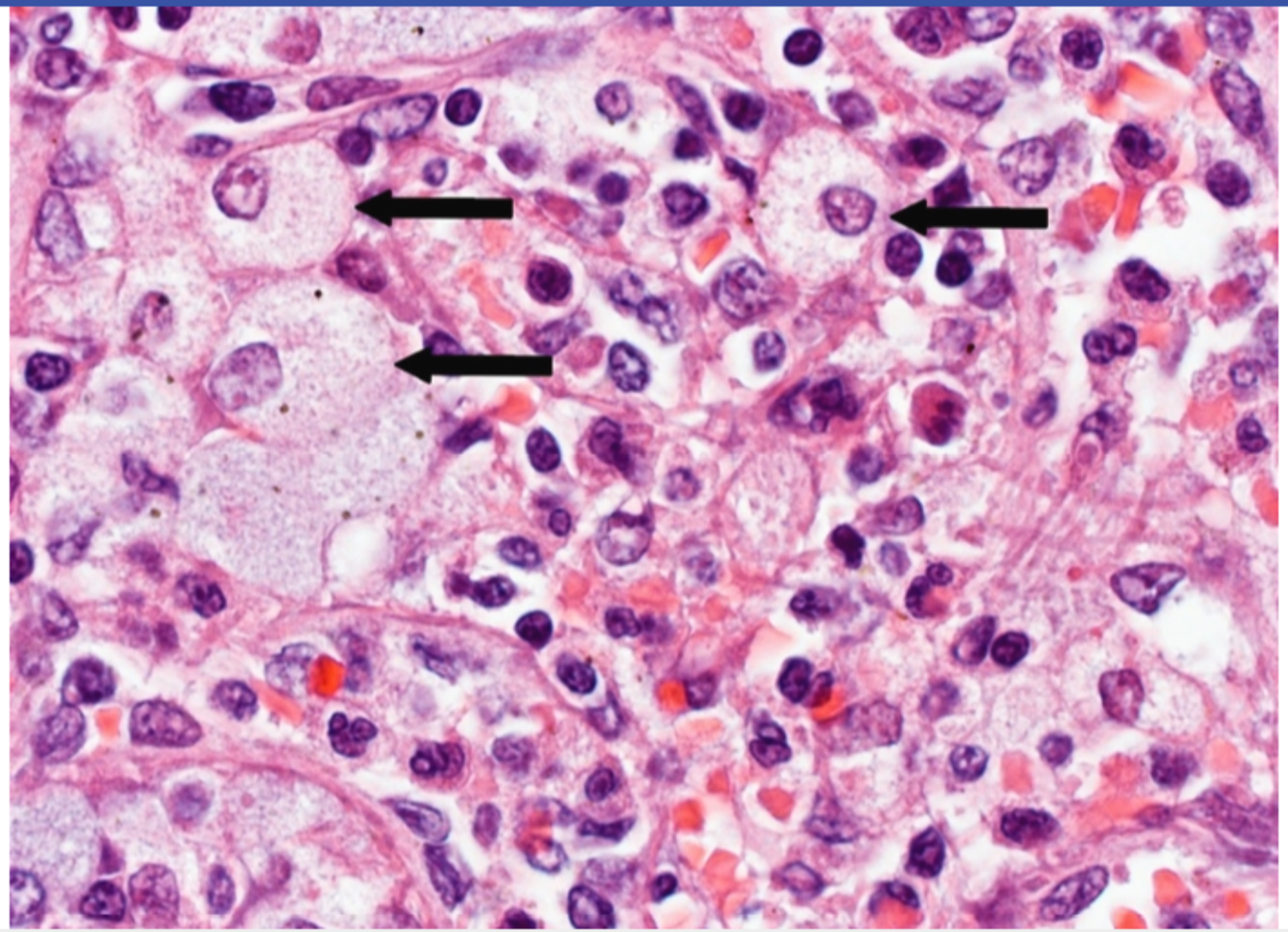

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References

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References

Niemann-Pick disease and other rare genetic disorders (eg, Tay-Sachs disease, Gaucher disease, Bloom syndrome) are more common among the **Ashkenazi Jewish** population. The increased risk of rare and often life-threatening genetic mutations is attributed to the "**founder effect**," which refers to the loss of genetic variability within a group that historically conceived within their own community. Prior to conceiving a child, an Ashkenazi Jewish couple should be offered **genetic counseling and testing**.

(Choice A) Gaucher disease, the most common genetic disorder among Ashkenazi Jews, is characterized by β-glucocerebrosidase deficiency and glucocerebroside accumulation. Typical features include hepatosplenomegaly, pancytopenia, and severe bone pain.

(Choice B) Hurler syndrome is a mucopolysaccharidosis that leads to dysostosis multiplex (eg, enlarged skull, abnormally shaped ribs and vertebrae) and corneal clouding, which can cause blindness. This disorder is characterized by accumulation of heparan sulfate and dermatan sulfate due to α-L-iduronidase deficiency.

(Choice D) In Fabry disease, α-galactosidase A deficiency causes globotriaosylceramide (ceramide trihexoside) accumulation. Disease manifestations include neuropathic pain and angiokeratomas in adolescence and multi-organ involvement (renal, cerebrovascular, cardiac) in adulthood.

(Choice E) Small stature and infertility along with a predisposition to malignancy and a classic sun-sensitive facial rash are typical signs of Bloom syndrome, an autosomal recessive disorder that leads to chromosomal instability.

Educational objective:
Niemann-Pick disease is an autosomal recessive disorder that is common in the Ashkenazi Jewish population. This disorder is characterized by sphingomyelinase deficiency and sphingomyelin accumulation, which cause hepatosplenomegaly and neurologic regression in infancy.

References

- Types A and B Niemann-Pick disease.

Biochemistry	Endocrine, Diabetes & Metabolism	Niemann pick
Subject	System	Topic

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A 12-year-old boy is brought to the office due to gait instability and pruritic skin rash for the past several weeks. His mother reports that he has also been irritable and had loose stools during this time. The patient's childhood development has been unremarkable except for several episodes of similar skin rash that resolved spontaneously. Examination shows scaly, erythematous skin lesions in sun-exposed areas and cerebellar ataxia. Laboratory evaluation shows increased levels of neutral amino acids in the urine. This patient's symptoms would most likely respond to which of the following supplements?

- A. Ascorbate
- B. Folic acid
- C. Niacin
- D. Pyridoxine
- E. Riboflavin
- F. Thiamine
- G. Tocopherol

Submit

A 12-year-old boy is brought to the office due to gait instability and pruritic skin rash for the past several weeks. His mother reports that he has also been irritable and had loose stools during this time. The patient's childhood development has been unremarkable except for several episodes of similar skin rash that resolved spontaneously. Examination shows scaly, erythematous skin lesions in sun-exposed areas and cerebellar ataxia. Laboratory evaluation shows increased levels of neutral amino acids in the urine. This patient's symptoms would most likely respond to which of the following supplements?

- A. Ascorbate (2%)
- B. Folic acid (2%)
- ✓ C. Niacin (55%)
- D. Pyridoxine (16%)
- E. Riboflavin (4%)
- F. Thiamine (11%)
- G. Tocopherol (6%)

Omitted
Correct answer
C

55%
Answered correctly

02 secs
Time Spent

04/25/2020
Last Updated

Explanation

This patient likely has **Hartnup disease**, an autosomal recessive metabolic disorder caused by inactivating mutations affecting the **neutral amino acid transporter**. This results in impaired transport of neutral amino acids, particularly tryptophan, in the small intestine and proximal tubule of

This patient likely has **Hartnup disease**, an autosomal recessive metabolic disorder caused by inactivating mutations affecting the **neutral amino acid transporter**. This results in impaired transport of neutral amino acids, particularly tryptophan, in the small intestine and proximal tubule of the kidney.

Tryptophan is an essential amino acid and a precursor for niacin, serotonin, and melatonin. Conversion of tryptophan to niacin is responsible for the generation of up to half of the nicotinamide adenine dinucleotide (NAD+) required for redox reactions; the clinical manifestations of Hartnup disease are primarily due to niacin deficiency. Patients present with intermittent attacks of **pellagra-like skin eruptions** (development of a red, rough rash following sun exposure) and **cerebellar ataxia** in early childhood that become less severe with increasing age.

The diagnosis is confirmed by detecting excessive amounts of neutral amino acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, and tryptophan) in the urine (**neutral aminoaciduria**). A high-protein diet along with daily niacin or nicotinamide supplementation generally results in significant symptom improvement.

(Choice A) Ascorbate (vitamin C) is a water-soluble vitamin required for hydroxylation of proline and lysine residues during collagen synthesis. Deficiency results in scurvy, a disease characterized by bone pain, easy bruising, and poor wound healing.

(Choice B) Both folic acid and vitamin B_{12} deficiencies result in a megaloblastic anemia. However, neurologic manifestations of subacute combined degeneration of the posterior and lateral columns are specific to vitamin B_{12} deficiency.

(Choice D) Pyridoxine (vitamin B_6) acts as a coenzyme in the decarboxylation and transamination of amino acids, including the metabolism of tryptophan to niacin. Deficiency of pyridoxine leads to anemia, peripheral neuropathy, and dermatitis. Supplementation in Hartnup disease is not effective due to underlying tryptophan malabsorption.

(Choice E) The coenzymes flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) form the prosthetic groups of several enzymes important in electron transport; both are synthesized from riboflavin (vitamin B_2). Clinical features of deficiency include sore throat, stomatitis, glossitis, normocytic anemia, and seborrheic dermatitis.

(Choice F) Thiamine use by the body is maximal in states of accelerated carbohydrate metabolism because thiamine acts as a cofactor for the enzymes transketolase (pentose phosphate pathway), α-ketoglutarate dehydrogenase (TCA cycle), and pyruvate dehydrogenase (forms acetyl-CoA).

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(Choice F) Thiamine use by the body is maximal in states of accelerated carbohydrate metabolism because thiamine acts as a cofactor for the enzymes transketolase (pentose phosphate pathway), α-ketoglutarate dehydrogenase (TCA cycle), and pyruvate dehydrogenase (forms acetyl-CoA).

(Choice G) Tocopherol (vitamin E) is a fat-soluble vitamin that functions as a scavenger of free radicals (antioxidant). Deficiency of vitamin E is rare but can result in neurologic dysfunction (ataxia, hyporeflexia, loss of sensation) as well as hemolytic anemia.

Educational objective:
Hartnup disease is caused by impaired transport of neutral amino acids in the small intestine and proximal tubule of the kidney. Symptoms include pellagra-like skin eruptions and cerebellar ataxia, which occur as a result of niacin deficiency. The diagnosis can be confirmed through detection of excessive amounts of neutral amino acids in the urine.

References

- Hartnup disease.
- Hartnup disorder: unraveling the mystery.

Biochemistry	Endocrine, Diabetes & Metabolism	Niacin deficiency
Subject	System	Topic

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A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

A. Galactose-1-phosphate uridyl transferase
B. Aldolase B
C. Fructokinase
D. Galactokinase
E. Acid α-glucosidase

Submit

A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

- A. Galactose-1-phosphate uridyl transferase (9%)
- ✓ B. Aldolase B (64%)
- C. Fructokinase (20%)
- D. Galactokinase (3%)
- E. Acid α-glucosidase (2%)

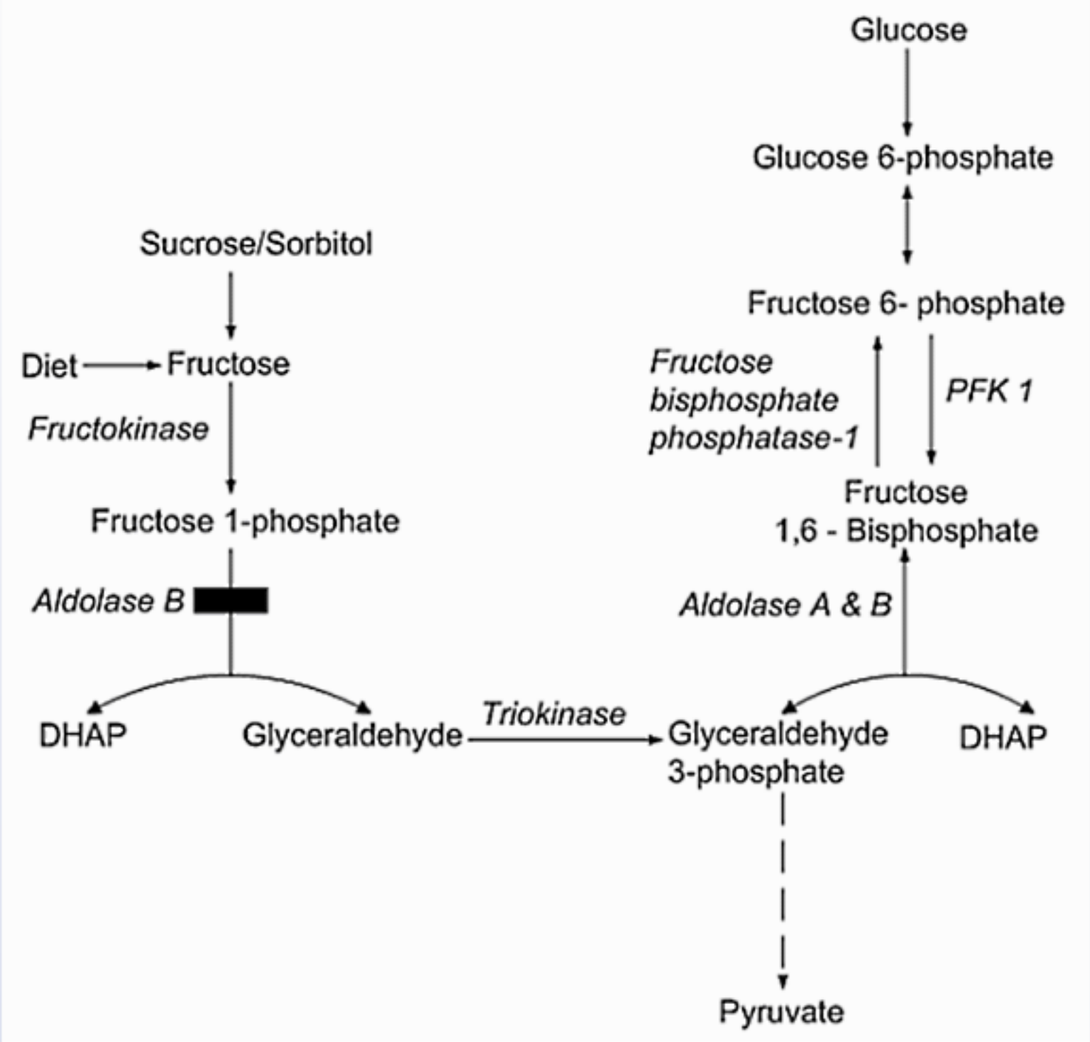
Omitted
Correct answer
B

64%
Answered correctly

02 secs
Time Spent

06/24/2020
Last Updated

Explanation



Dietary fructose is obtained mainly from fruits, vegetables, honey, table sugar (sucrose), and processed foods. Fructose is rapidly absorbed in the

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Dietary fructose is obtained mainly from fruits, vegetables, honey, table sugar (sucrose), and processed foods. Fructose is rapidly absorbed in the proximal small bowel by the hexose transporter GLUT 5. Initial metabolism of fructose involves three enzymes: fructokinase, aldolase B, and triokinase. Fructose is phosphorylated on the first carbon by hepatic fructokinase, yielding fructose-1-phosphate. Metabolism of fructose-1-phosphate by aldolase B generates dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde is then phosphorylated to glyceraldehyde-3-phosphate (G3P), an intermediate of glycolysis, by triose kinase. DHAP can also be converted to G3P by triose phosphate isomerase.

Aldolase B deficiency causes the potentially life-threatening disorder known as hereditary fructose intolerance. Patients typically present when fructose-containing foods are introduced into the diet. The primary manifestations are vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. Hypoglycemia results from intracellular accumulation of fructose-1-phosphate and depletion of inorganic phosphate, which inhibit glycogenolysis and gluconeogenesis. Failure to thrive, hepatomegaly, and jaundice can also occur. Undiagnosed individuals may eventually develop liver and renal failure. Elimination of dietary fructose is the mainstay of treatment and results in symptom improvement with a good long-term prognosis.

(Choices A and D) Galactose-1-phosphate uridyl transferase deficiency (classic galactosemia) is an autosomal recessive disorder characterized by vomiting, feeding intolerance, neonatal jaundice, hepatomegaly, and death if untreated. Symptoms start soon after breastfeeding is initiated. Galactokinase deficiency is a more benign disorder of galactose metabolism that results in the formation of neonatal cataracts.

(Choice C) Fructokinase deficiency causes essential fructosuria, a benign autosomal recessive disorder. Fructose from the diet is absorbed and secreted freely in the urine due to impairment of the first step in fructose metabolism.

(Choice E) Glycogenolysis is accomplished mainly by glycogen phosphorylase and debranching enzyme, but a small amount is also broken down by the lysosomal enzyme α-1,4-glucosidase. Alpha-glucosidase (or acid maltase) deficiency causes Pompe disease. This disease presents not with hypoglycemia, but with cardiomyopathy and hypotonia.

Educational objective:
Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly.

Biochemistry Endocrine, Diabetes & Metabolism Fructose metabolism

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Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly.

Biochemistry	Endocrine, Diabetes & Metabolism	Fructose metabolism
Subject	System	Topic

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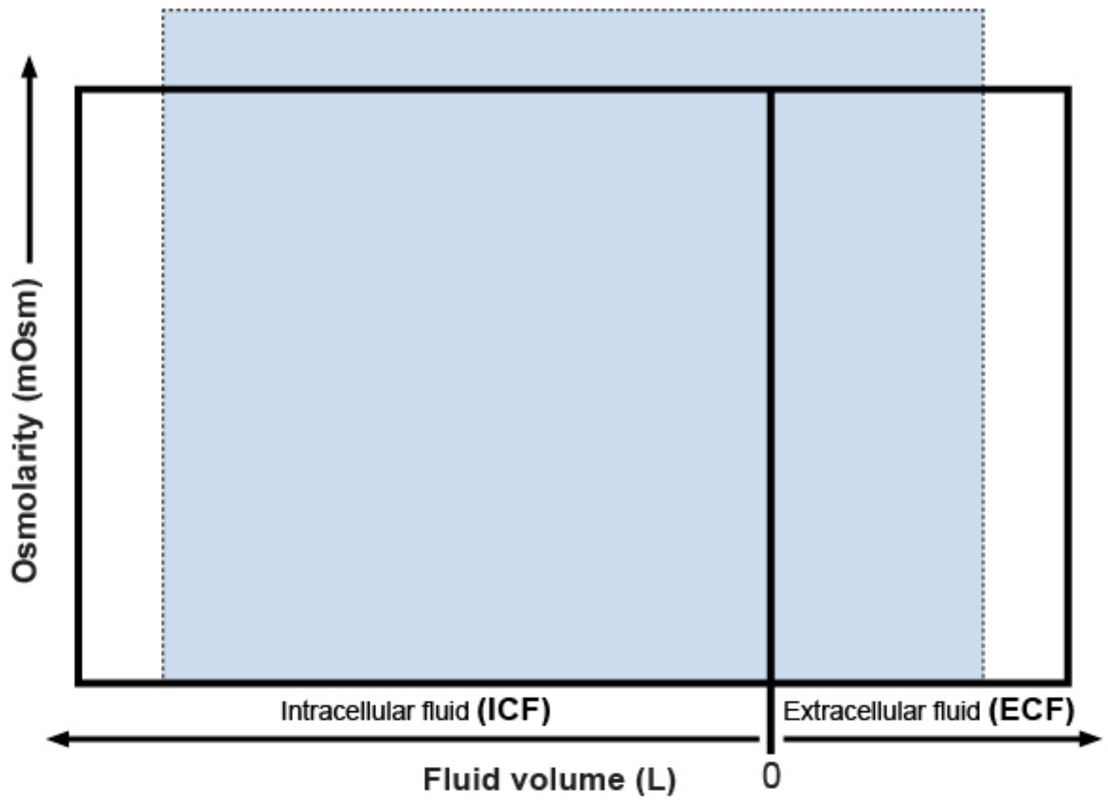
A 23-year-old man is brought to the emergency department by paramedics following a motor vehicle accident. He was an unrestrained passenger in the front seat. Several days after hospitalization, his fluid volume and plasma osmolarity are measured and illustrated in the image below (solid line, normal; dotted line, patient).



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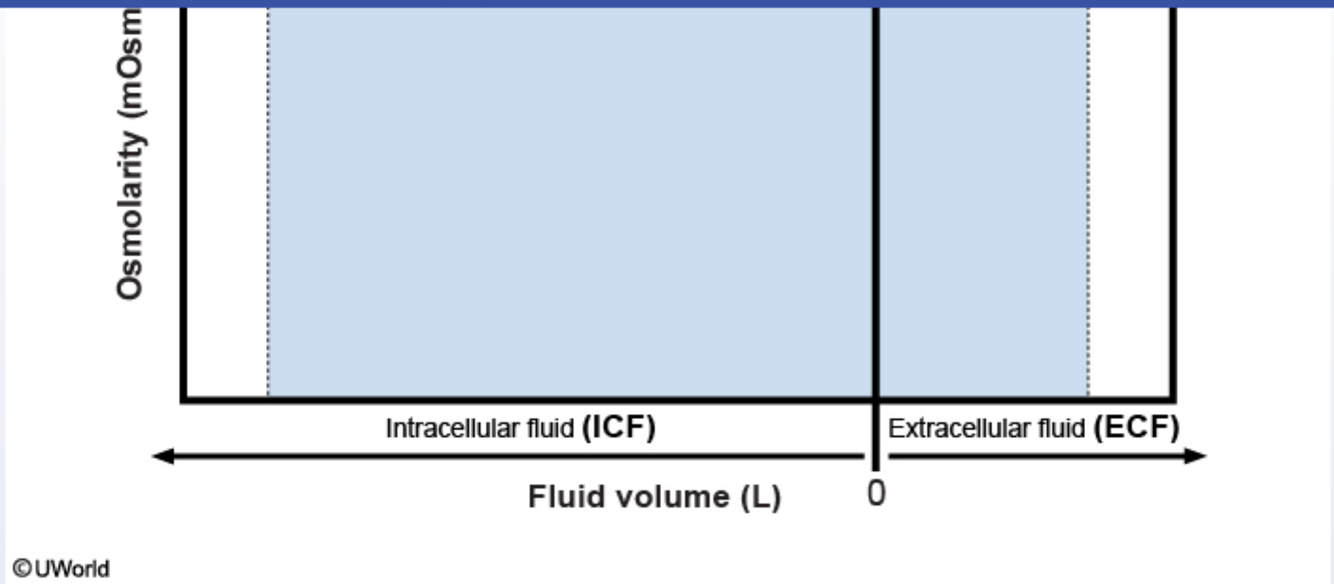

Which of the following conditions is most likely to cause the findings shown in the image?

A. Acute gastrointestinal hemorrhage

B. Adrenal insufficiency

C. Diabetes insipidus

D. Hypertonic saline infusion

E. Primary polydipsia

Submit

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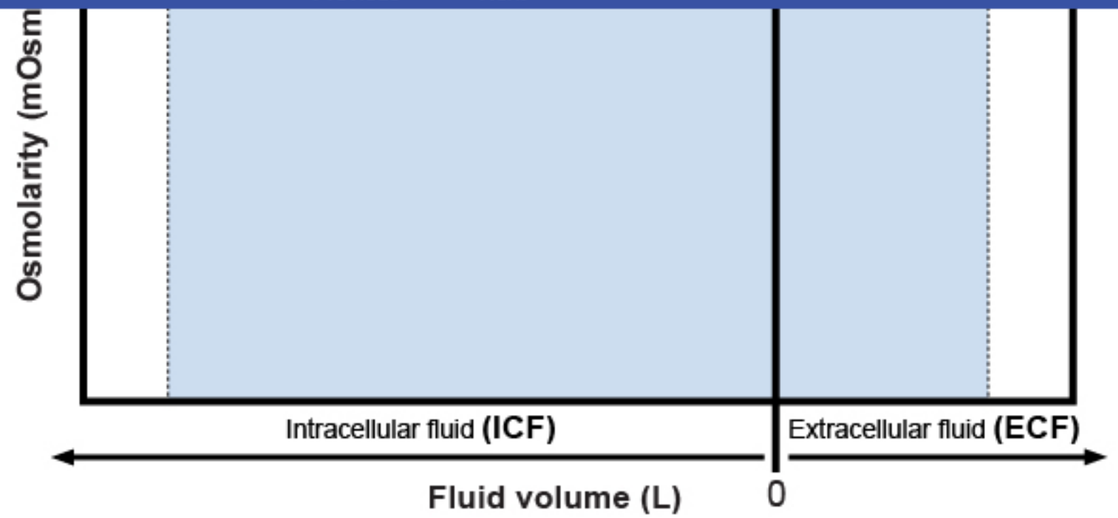

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Which of the following conditions is most likely to cause the findings shown in the image?

A. Acute gastrointestinal hemorrhage (17%)

B. Adrenal insufficiency (7%)

✓ C. Diabetes insipidus (55%)

D. Hypertonic saline infusion (14%)

E. Primary polydipsia (3%)

Omitted
Correct answer

55%
Answered correctly

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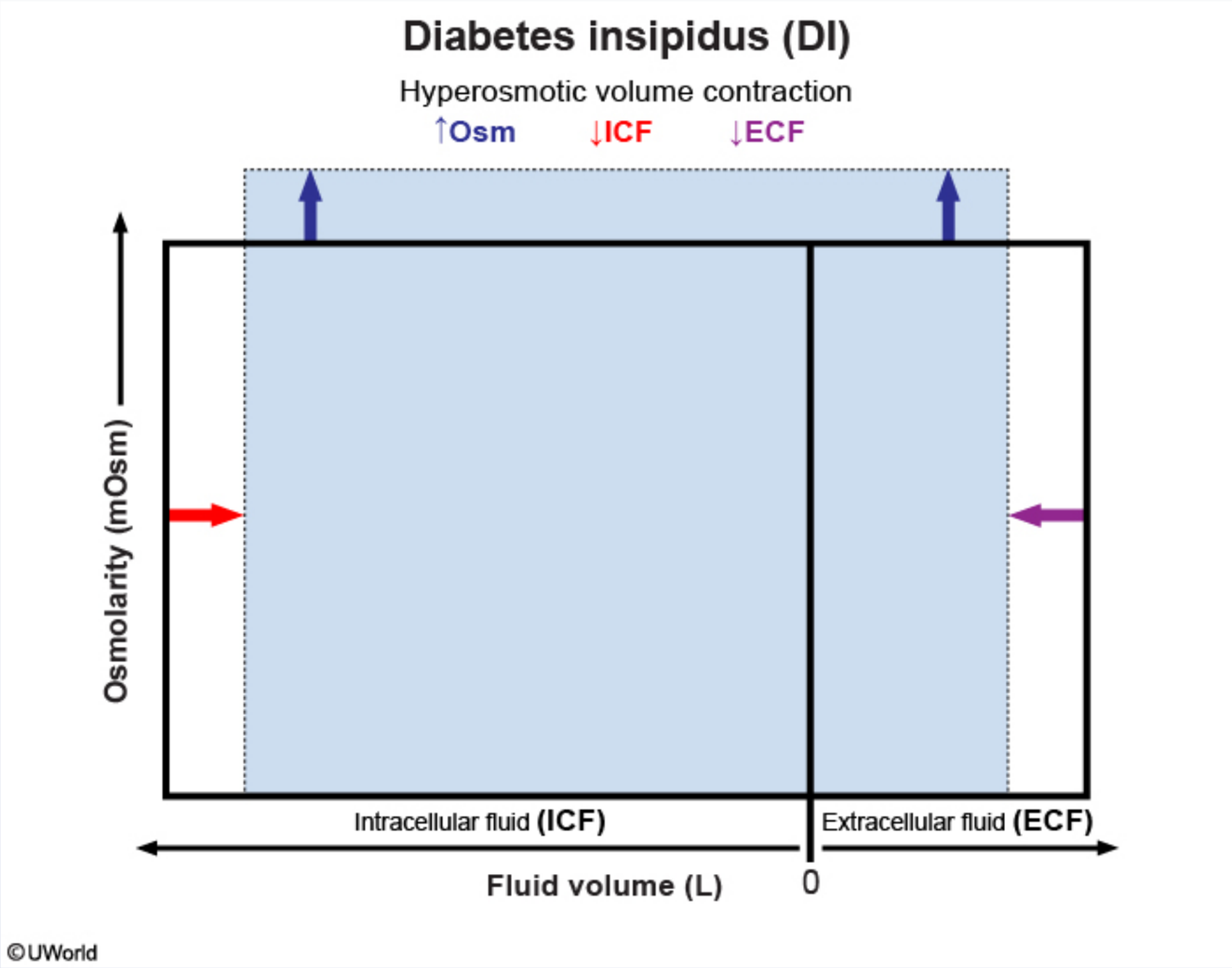
Time Spent

03/03/2020
Last Updated

Explanation



The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those compartments (y-axis).

This patient's recent head trauma is consistent with central diabetes insipidus due to hypothalamic/pituitary damage. The resulting decrease in vasopressin secretion leads to excessive free water excretion by the kidneys, causing **hyperosmotic volume contraction**. This condition occurs when the loss of free water exceeds the loss of electrolytes, resulting in increased osmolarity and contracted volumes in both the ICF and ECF compartments. Hyperosmotic volume contraction can occur in the setting of **diabetes insipidus**, decreased fluid intake (**dehydration**), and with **profuse sweating** (due to the hypotonic nature of sweat).

(Choice A) Acute gastrointestinal hemorrhage (or diarrhea) would cause an isotonic loss of ECF volume, with no effects on osmolarity or ICF volume. This is referred to as isosmotic volume contraction.

(Choice B) The lack of aldosterone in adrenal insufficiency causes loss of NaCl with ECF volume depletion (hyposmotic volume contraction). The low osmolarity of the ECF results in shifting of free water into the ICF compartment, causing ICF expansion.

(Choice D) Infusion of large amounts of hypertonic saline leads to hypertonic volume expansion. Both the volume and osmolarity of the ECF are increased. The high osmolarity of the ECF leads to shifting of water from the ICF, further increasing the ECF volume.

(Choice E) Primary polydipsia (excessive water consumption) and SIADH (inappropriately high vasopressin levels) both cause retention of free water in the body. This leads to expansion of the ICF compartment and a decrease in the osmolarity of both compartments (hyposmotic volume expansion). Expansion of the ECF compartment is limited in these conditions due to compensatory secretion of aldosterone and natriuretic peptides, which help to normalize the extracellular fluid volume. Thus, affected patients are clinically euvolemic.

Educational objective:
Volume contraction and expansion can be divided into isosmotic, hyposmotic, and hyperosmotic states. Hyperosmotic volume contraction is caused by a loss of free water (with retention of electrolytes). It can occur in patients with diabetes insipidus or as a result of decreased fluid intake/excessive sweating.

Biochemistry	Endocrine, Diabetes & Metabolism	Body fluid distribution
Subject	System	Topic

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those

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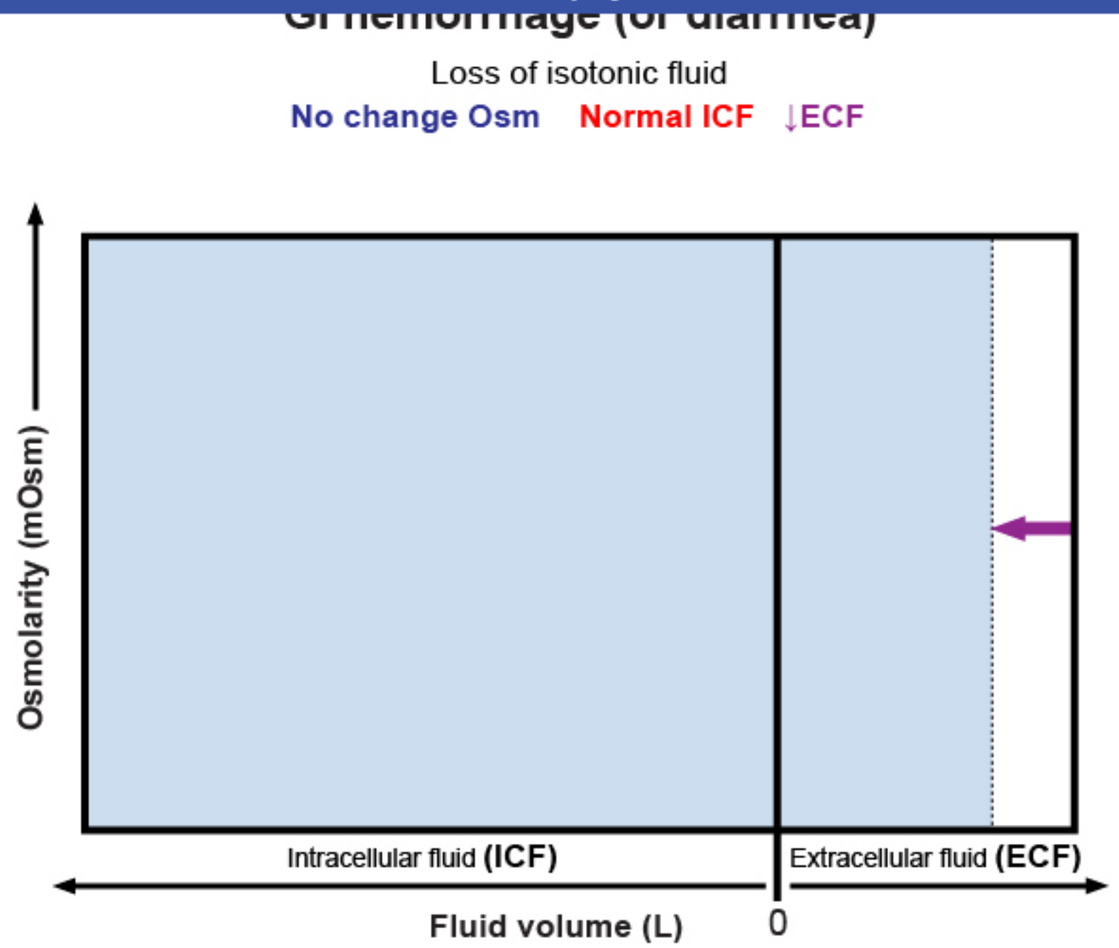

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Subject System Topic

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those

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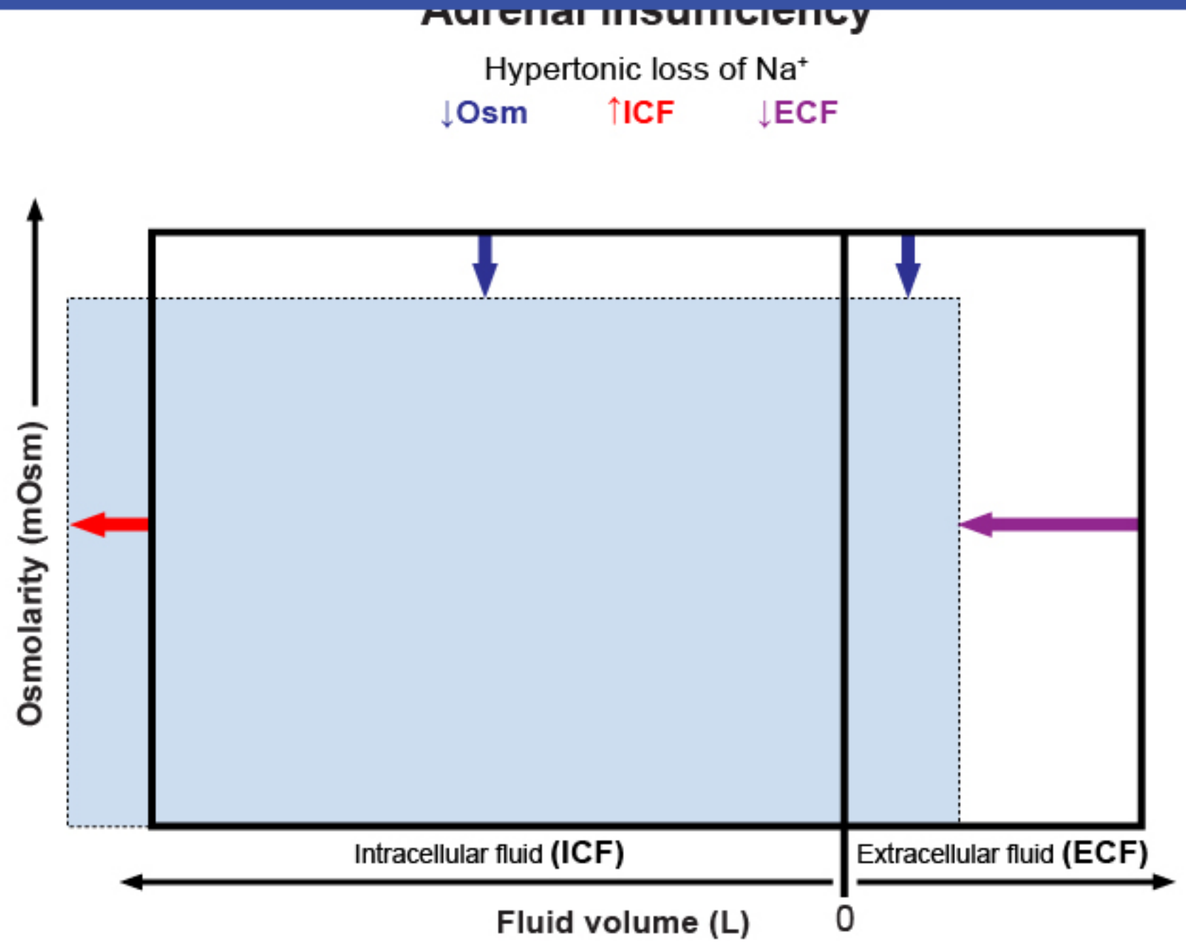

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Subject System Topic

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those

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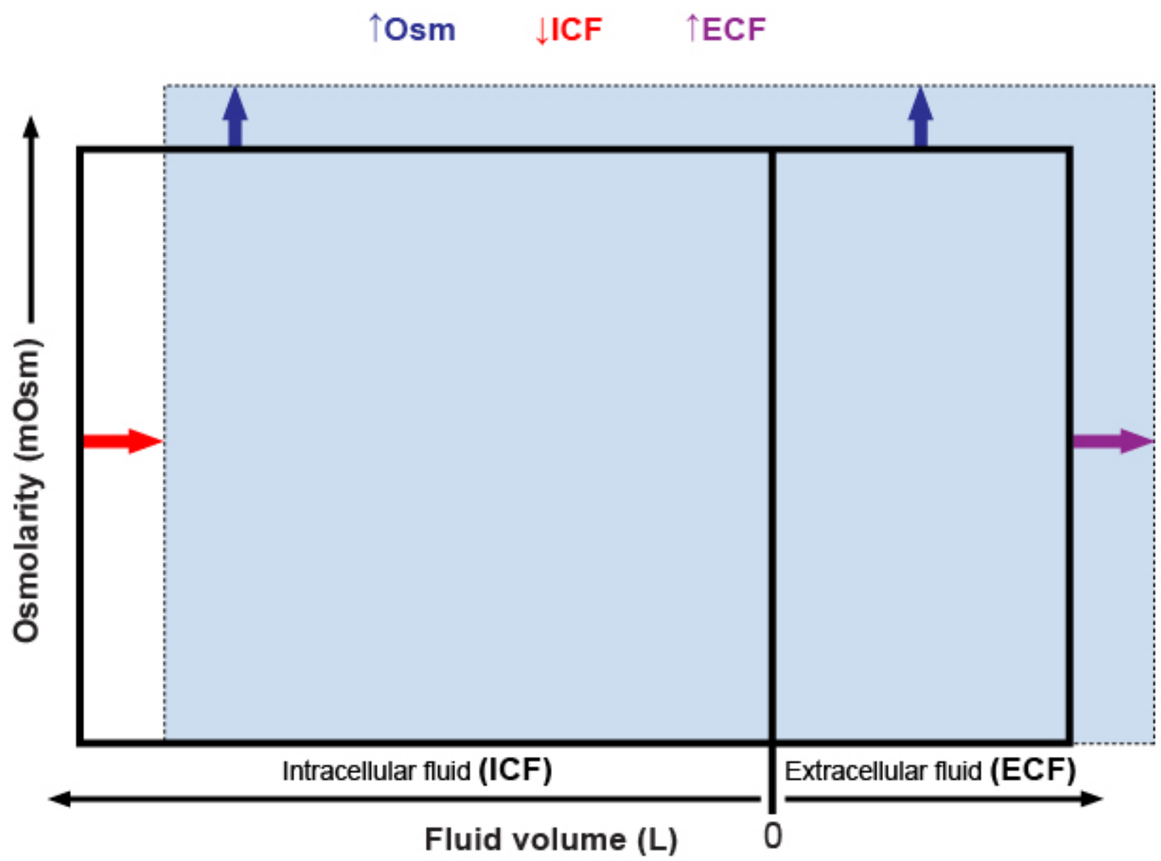

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Subject System Topic

The figure shows the volume of the intracellular (ICF) and extracellular (ECF) fluid compartments (x-axis) and the osmolarity of the fluid in those

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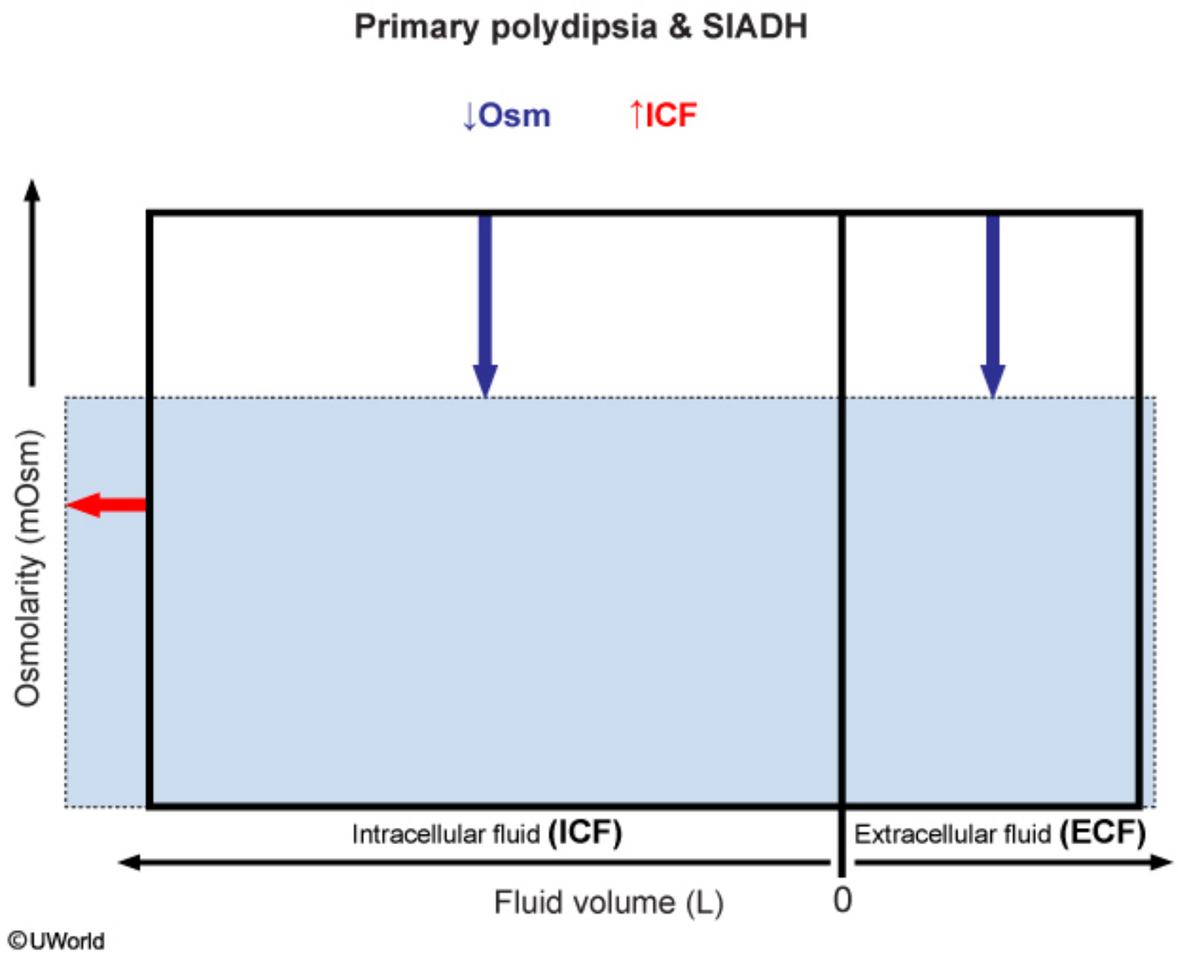

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Subject System Topic

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A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

A. Anchoring to the cell membrane

B. Binding to an extracellular ligand

C. Binding to intranuclear DNA

D. Interacting with metal ions in transporting proteins

E. Phosphorylating tyrosine residues

Submit

A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

- ✓ A. Anchoring to the cell membrane (46%)
- B. Binding to an extracellular ligand (15%)
- C. Binding to intranuclear DNA (18%)
- D. Interacting with metal ions in transporting proteins (7%)
- E. Phosphorylating tyrosine residues (11%)

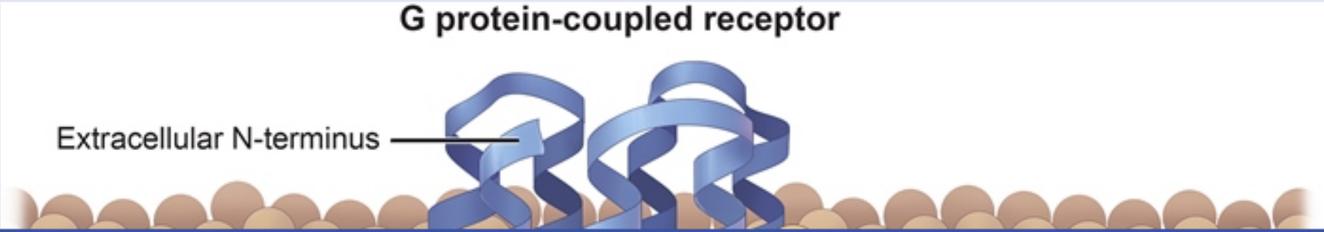
Omitted
Correct answer
A

46%
Answered correctly

02 secs
Time Spent

04/15/2020
Last Updated

Explanation



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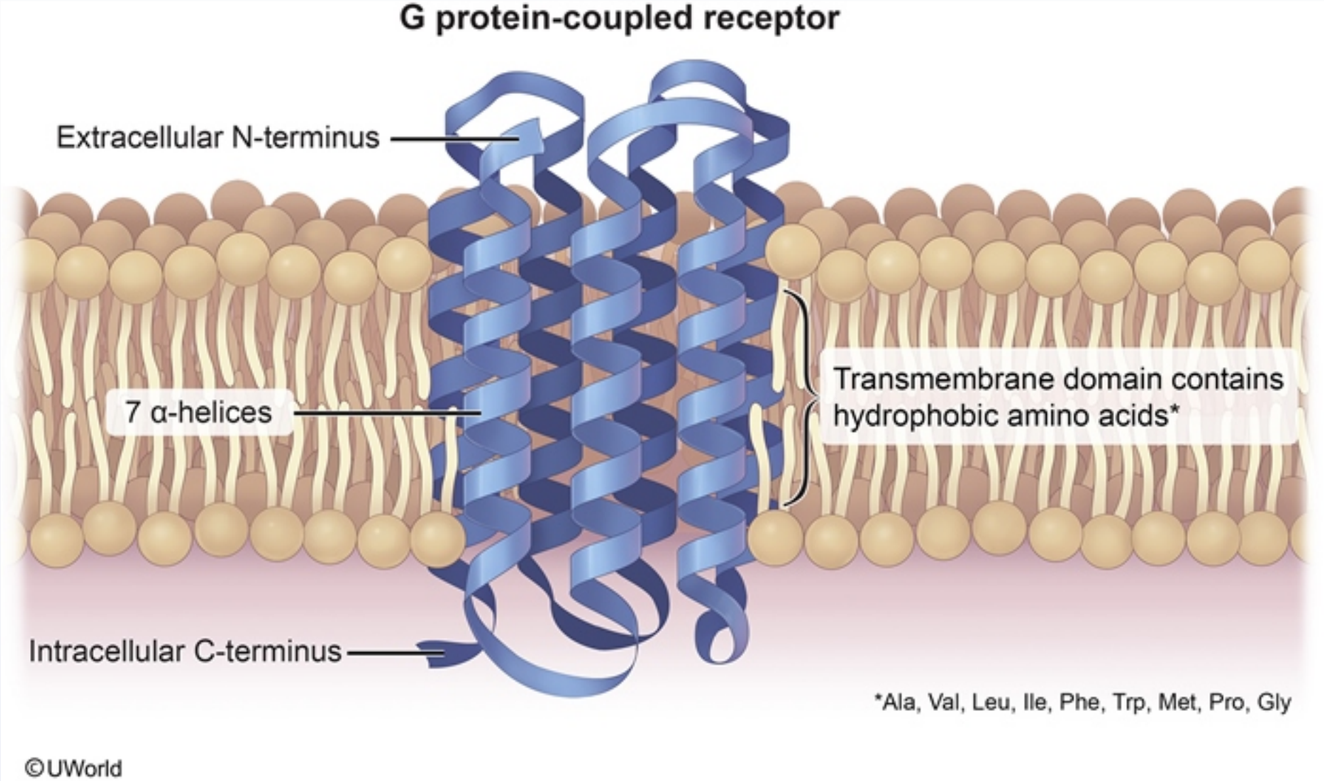

G protein-coupled receptors that bind glycoprotein hormones (eg, TSH, LH, FSH) contain 3 major domains: an extracellular domain responsible for ligand binding, a transmembrane domain, and an intracellular domain coupled with heterotrimeric G proteins.

The **transmembrane domain** is made up of **nonpolar, hydrophobic amino acids** (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These amino acids are arranged in an alpha-helical fashion and project their hydrophobic R groups outwardly, **anchoring** the transmembrane region of the protein to the hydrophobic core of the **phospholipid bilayer**. The transmembrane domain may also play an important role in cellular signaling and transport.

(Choice B) Binding of a ligand to the extracellular domain of a transmembrane receptor can result in activation of the cAMP or

G protein-coupled receptors that bind glycoprotein hormones (eg, TSH, LH, FSH) contain 3 major domains: an extracellular domain responsible for ligand binding, a transmembrane domain, and an intracellular domain coupled with heterotrimeric G proteins.

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(Choice B) Binding of a ligand to the extracellular domain of a transmembrane receptor can result in activation of the cAMP or phosphatidylinositol second messenger system, activation of receptor tyrosine kinases, opening of ion channels, and activation of the calcium-calmodulin system. The extracellular domain of these receptors is typically composed of hydrophilic amino acids.

(Choice C) Activation of G protein-coupled receptors utilizing the cAMP second messenger system results in increased synthesis of intracellular cAMP and subsequent activation of protein kinase A. Protein kinase A then phosphorylates cytosolic proteins that translocate into the nucleus and bind to DNA promoter regions to modulate transcription.

(Choice D) Intracellular iron-containing proteins (hemeproteins) include hemoglobin, myoglobin, and cytochrome oxidase. Heme is a complex of protoporphyrin IX and iron. Hemoglobin A, the most common hemoglobin in adults, consists of 2 alpha and 2 beta globin chains held together by noncovalent interactions. Each subunit contains stretches of alpha helices that form a heme-binding pocket lined by nonpolar amino acids.

(Choice E) Insulin and IGF-1 bind to receptors that possess tyrosine kinase on their intracellular domain (receptor tyrosine kinases). These receptors dimerize upon ligand binding to the extracellular domain, which subsequently activates tyrosine kinase. Tyrosine kinase phosphorylates tyrosine residues, triggering a downstream cellular response.

Educational objective:
Integral membrane proteins contain transmembrane domains composed of alpha helices with hydrophobic amino acid residues (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These transmembrane domains help anchor the protein to the phospholipid bilayer of the cell membrane.

References

- G protein coupled receptor structure and activation.

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References

- G protein coupled receptor structure and activation.
- Transmembrane domains participate in functions of integral membrane proteins.

Biochemistry	Endocrine, Diabetes & Metabolism	Protein structure
Subject	System	Topic

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A 6-month-old girl is brought to the office by her mother for a checkup appointment. The mother states, "My baby doesn't seem to be growing much despite feeding as often as my previous children. I am worried that something is wrong with her." Physical examination shows hepatomegaly, hypotonia, and height and weight below the 10th percentile. Laboratory studies show hypoglycemia and ketoacidosis. A liver biopsy shows hepatic fibrosis without fat accumulation. Further analysis reveals abundant quantities of a multibranched polysaccharide with abnormally short outer chains within the cytosol of the hepatocytes. Which of the following enzymes is most likely deficient in this patient?

A. Acid maltase
B. Debranching enzyme
C. Glucose-6-phosphatase
D. Liver glycogen phosphorylase
E. Muscle glycogen phosphorylase
F. Pyruvate kinase

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- A. Acid maltase (2%)
- ✓ B. Debranching enzyme (69%)
- C. Glucose-6-phosphatase (13%)
- D. Liver glycogen phosphorylase (10%)
- E. Muscle glycogen phosphorylase (1%)
- F. Pyruvate kinase (1%)

Omitted
Correct answer
B

69%
Answered correctly

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Last Updated

Explanation

Impairments in glycogenolysis

1,4-α-glycosidic bond

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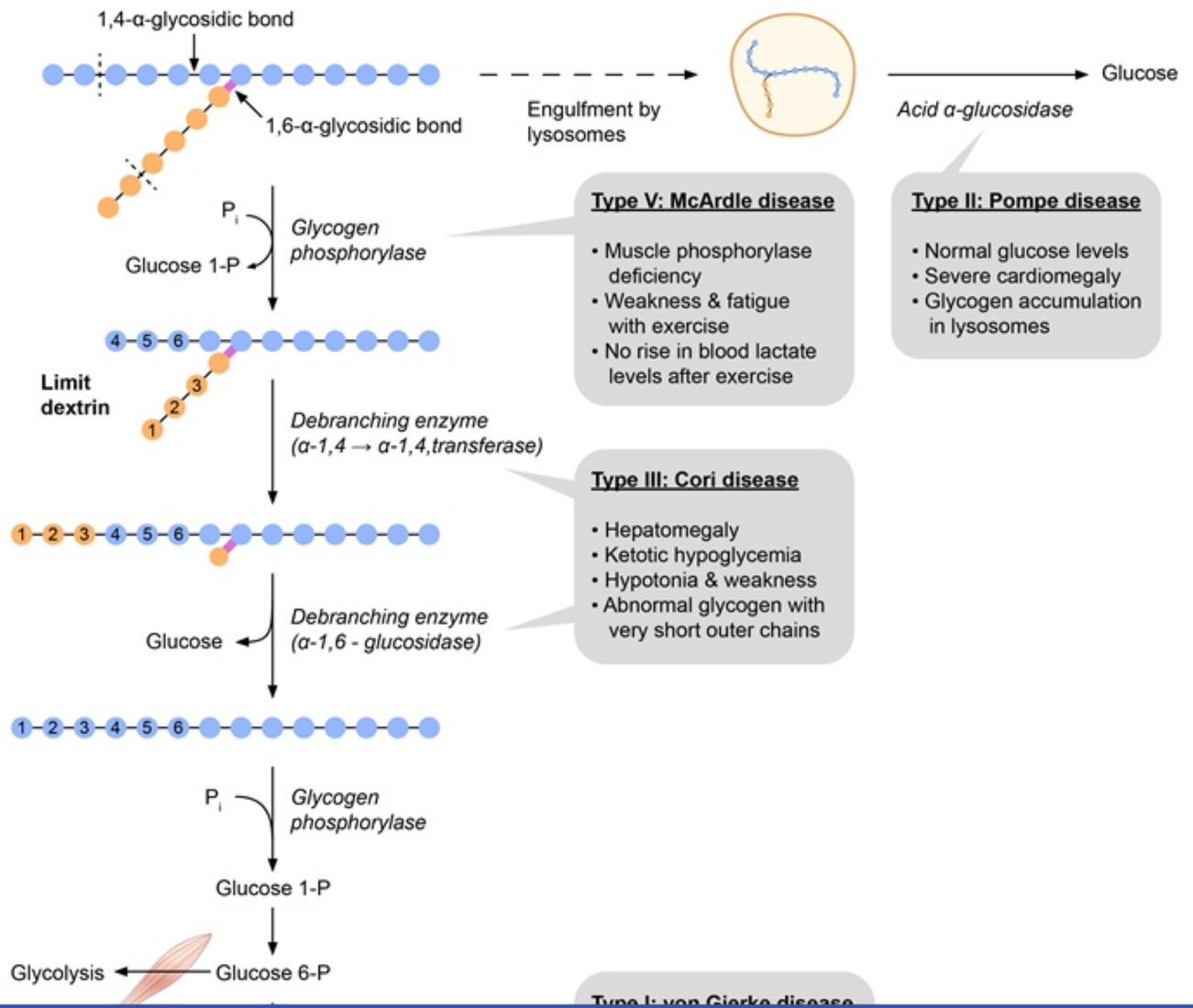
Impairments in glycogenolysis



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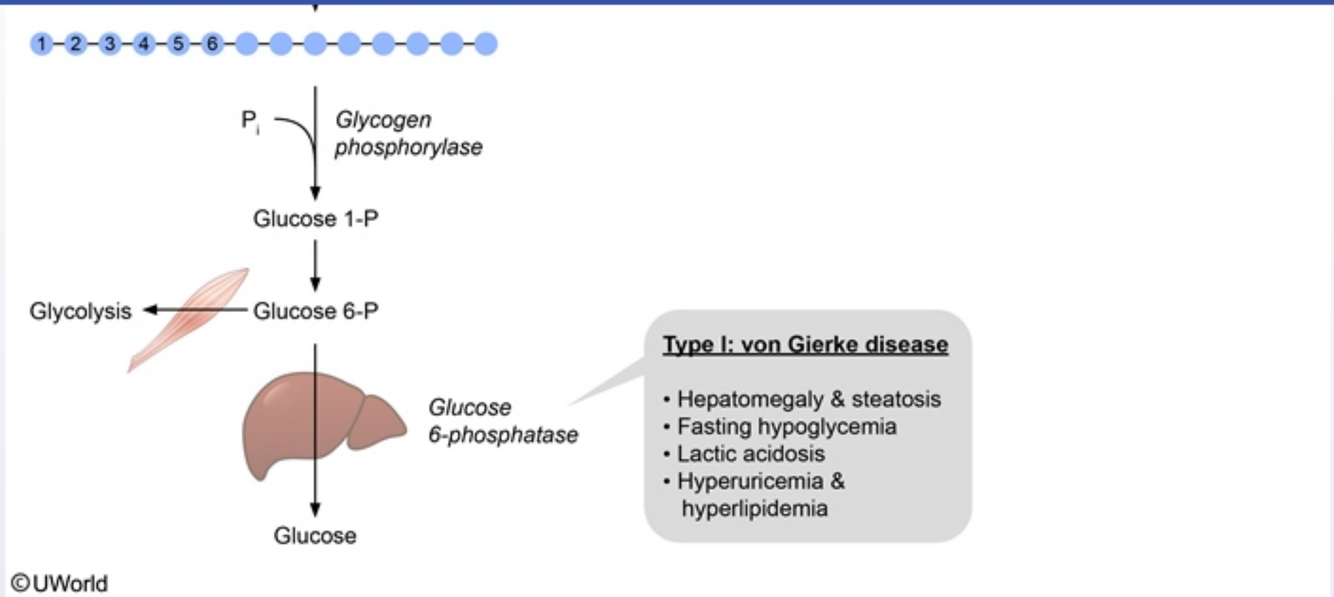

Debranching enzyme deficiency (Cori disease) usually presents in infancy or childhood with both liver and muscle involvement. Symptoms include **hypoglycemia**, **hepatomegaly**, and ketoacidosis. Muscle weakness and **hypotonia** help to distinguish the condition from other glycogen storage diseases with hepatic involvement (eg, von Gierke, Hers). Hepatic fibrosis is common, but fatty infiltration is not usually seen. A key distinguishing feature is cytosolic accumulation of glycogen with abnormally **short outer chains** (limit dextrins).

During glycogenolysis, glycogen phosphorylase shortens glycogen chains by cleaving α-1,4-glycosidic linkages between glucose residues, liberating glucose-1-phosphate in the process. This occurs until 4 residues remain before a branch point (the limit dextrin). At this point, **debranching enzyme** performs 2 enzymatic functions:

1. Glucosyltransferase cleaves the outer 3 residues of the 4 glucose residues left by glycogen phosphorylase and transfers them to a nearby branch
2. α-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

(Choice A) Small amounts of glycogen are broken down by the lysosomal enzyme acid maltase (has both α-1,4- and α-1,6-glucosidase activity)

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(Choice A) Small amounts of glycogen are broken down by the lysosomal enzyme acid maltase (has both α-1,4- and α-1,6-glucosidase activity). Acid maltase deficiency (Pompe disease) is characterized by cardiomegaly, severe generalized hypotonia, and lysosomal glycogen accumulation (hypoglycemia is not seen).

(Choice C) Glucose-6-phosphatase deficiency (von Gierke disease) affects mainly the liver and kidney, as the enzyme is not expressed in significant quantities in muscle tissue. Major symptoms include hypoglycemia, lactic acidosis, hyperlipidemia, and hyperuricemia. Hepatic steatosis is a cardinal manifestation of the disorder.

(Choice D) Liver glycogen phosphorylase deficiency (Hers disease) presents in early childhood with mild hypoglycemia, ketosis, and hepatomegaly. However, it does not affect skeletal muscles and would show an excess of normally structured glycogen (not limit dextrins) on liver biopsy.

(Choice E) Muscle glycogen phosphorylase deficiency causes McArdle disease, a condition that presents with decreased exercise tolerance, muscle pain and cramping during strenuous activity, and myoglobinuria. Blood lactate is often very low after exercise, and muscle biopsy shows an excess of normally structured glycogen.

(Choice F) Pyruvate kinase converts phosphoenolpyruvate to pyruvate during glycolysis. Pyruvate kinase deficiency causes chronic hemolytic

shortened by glycogen phosphorylase

(Choice A) Small amounts of glycogen are broken down by the lysosomal enzyme acid maltase (has both α-1,4- and α-1,6-glucosidase activity). Acid maltase deficiency (Pompe disease) is characterized by cardiomegaly, severe generalized hypotonia, and lysosomal glycogen accumulation (hypoglycemia is not seen).

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(Choice E) Muscle glycogen phosphorylase deficiency causes McArdle disease, a condition that presents with decreased exercise tolerance, muscle pain and cramping during strenuous activity, and myoglobinuria. Blood lactate is often very low after exercise, and muscle biopsy shows an excess of normally structured glycogen.

(Choice F) Pyruvate kinase converts phosphoenolpyruvate to pyruvate during glycolysis. Pyruvate kinase deficiency causes chronic hemolytic anemia as glycolysis is the main source of energy for erythrocytes.

Educational objective:
Debranching enzyme deficiency (Cori disease) leads to accumulation of glycogen with abnormally short outer chains (limit dextrins) due to the inability to degrade α-1,6-glycosidic branch points. Patients present with hypoglycemia, ketoacidosis, hepatomegaly, and muscle weakness and hypotonia.

Biochemistry	Endocrine, Diabetes & Metabolism	Glycogen storage disease
Subject	System	Topic

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As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

A. 3-Hydroxy-3-methylglutaryl-CoA lyase

B. Ornithine transcarbamylase

C. Pyruvate carboxylase

D. Succinate dehydrogenase

E. Transketolase

Submit

As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

A. 3-Hydroxy-3-methylglutaryl-CoA lyase (10%)

B. Ornithine transcarbamylase (18%)

C. Pyruvate carboxylase (26%)

D. Succinate dehydrogenase (6%)

✓ E. Transketolase (37%)

Omitted
Correct answer
E

37%
Answered correctly

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Time Spent

04/22/2020
Last Updated

Explanation

Enzymes and the biochemical processes they catalyze often require distinct chemical environments for optimal function; small variations in temperature, molecular concentrations, and pH may render them ineffective. **Cellular compartmentalization** provides a means by which multiple heterogeneous environments can exist within a cell. Organelles such as the nucleus and mitochondria form distinct, membrane-bound regions with a chemical composition different from the cytosol. This allows multiple biochemical processes to occur simultaneously at maximum efficiency.

The cytosol and mitochondria are the predominant sites of metabolism in the cell. Mitochondria are the site of beta-oxidation of fatty acids, the

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The cytosol and mitochondria are the predominant sites of metabolism in the cell. Mitochondria are the site of beta-oxidation of fatty acids, the citric acid cycle, and the carboxylation of pyruvate (gluconeogenesis). The **cytosol** is home to enzymes necessary for glycolysis, fatty acid synthesis, and the **pentose phosphate pathway**. **Transketolase** is an enzyme of the pentose phosphate pathway that uses thiamine (vitamin B_1) as a cofactor to shuttle 2-carbon fragments between sugar molecules. Other processes such as heme synthesis, the urea cycle, and gluconeogenesis rely on a complex interplay between the mitochondria and cytosol to function optimally; enzymes present in both cellular compartments are required for these metabolic pathways.

(Choice A) 3-Hydroxy-3-methylglutaryl-CoA (HMG CoA) lyase is a mitochondrial enzyme necessary for ketogenesis. It is also responsible for metabolism of the ketogenic amino acid, leucine.

(Choice B) Ornithine transcarbamylase catalyzes the combination of ornithine and carbamoyl phosphate to form citrulline in the urea cycle. This reaction occurs within the mitochondria.

(Choice C) Pyruvate carboxylase catalyzes the initial step in gluconeogenesis by converting pyruvate to oxaloacetate. This enzyme requires biotin as a cofactor, and functions within the mitochondria.

(Choice D) Succinate dehydrogenase is a TCA cycle enzyme that converts succinate to fumarate. It is an inner mitochondrial membrane protein and functions as part of the electron transport chain.

Educational objective:
Cellular compartmentalization allows multiple biochemical processes to occur simultaneously at maximum efficiency. Beta-oxidation of fatty acids, the TCA cycle, and the carboxylation of pyruvate (gluconeogenesis) all occur within the mitochondria. The enzymes responsible for glycolysis, fatty acid synthesis, and the pentose phosphate pathway reside in the cytosol.

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Biochemistry	Endocrine, Diabetes & Metabolism	Principles of cell biology
Subject	System	Topic

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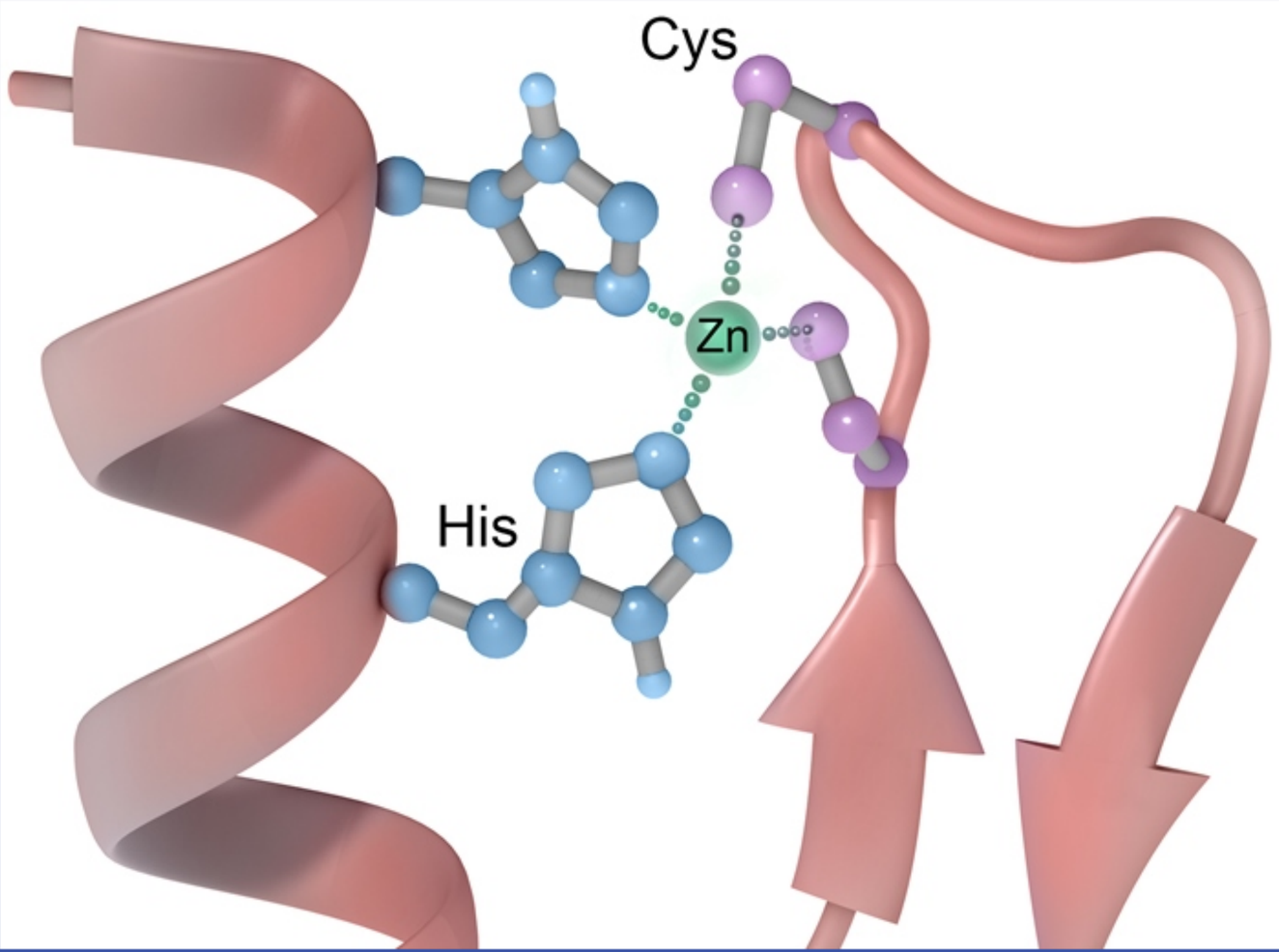
A researcher is studying the structure of different hormone receptors. Receptor proteins are isolated and purified from a homogenized tissue sample. Detailed structural analysis shows that one of the proteins contains a 30-amino acid motif coordinating a zinc molecule, as shown in the image below.



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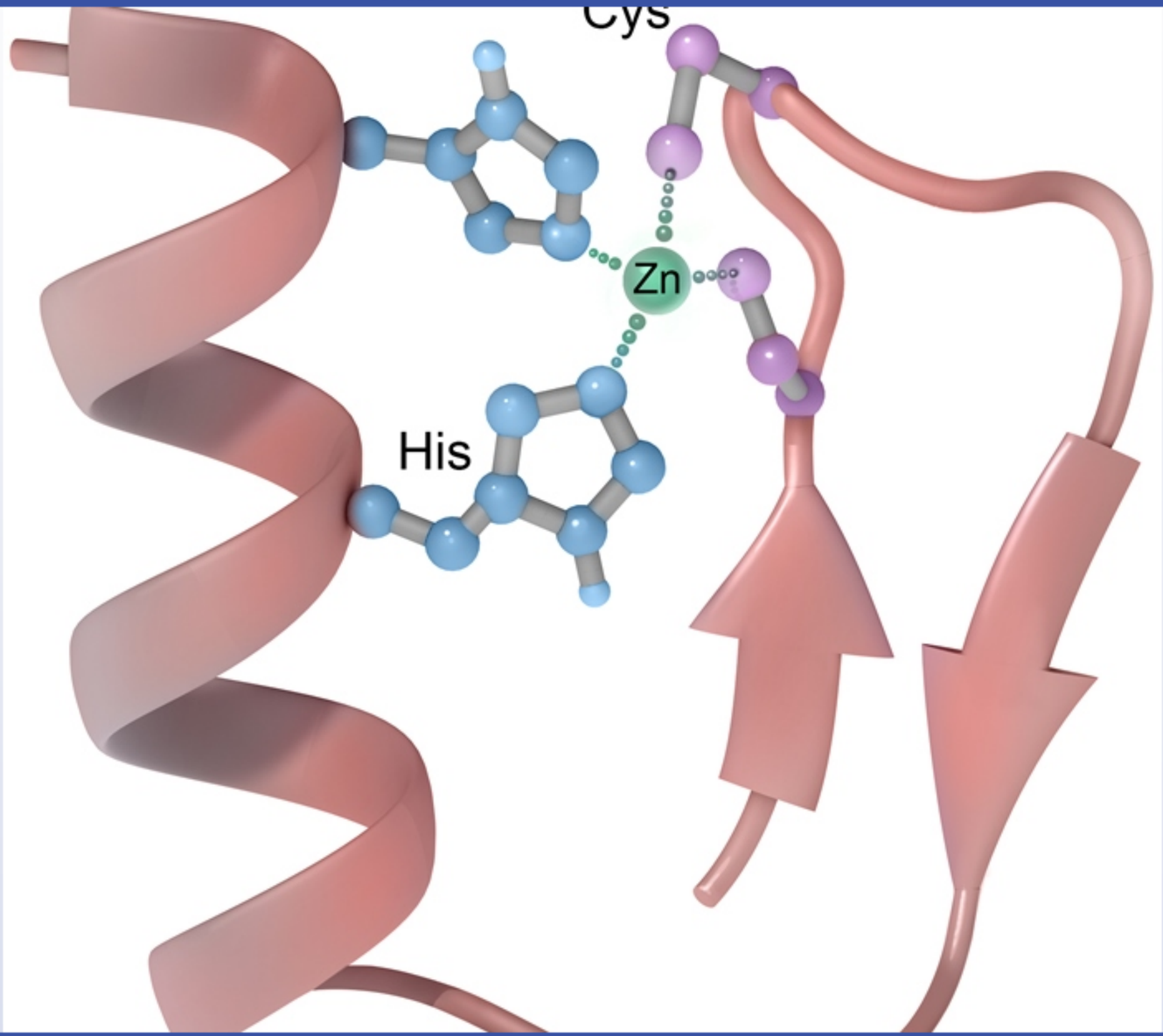

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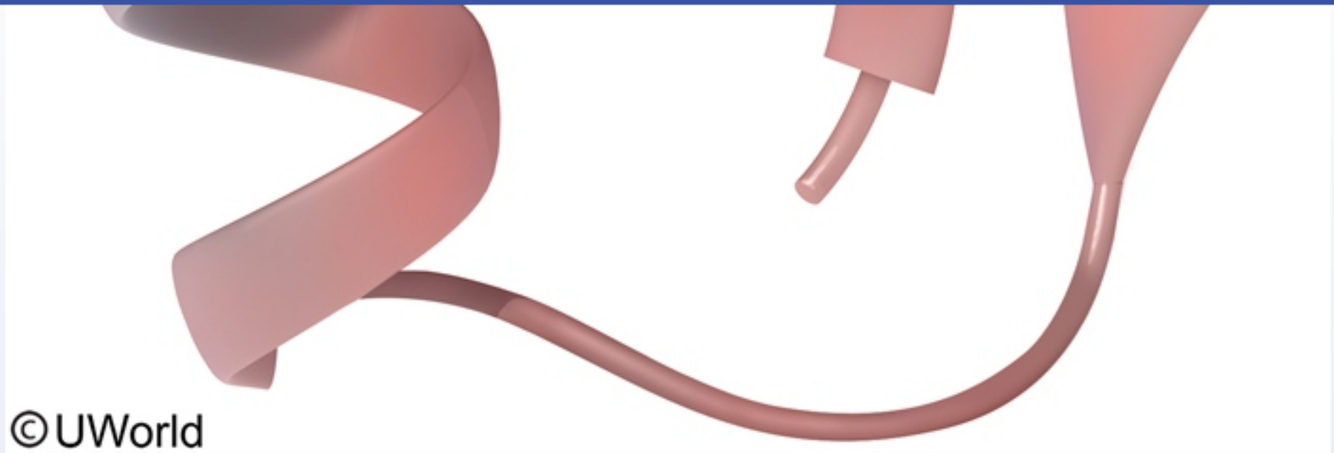

A receptor for which of the following hormones was most likely isolated in this experiment?

- A. Adrenocorticotropic hormone
- B. Antidiuretic hormone
- C. Epinephrine
- D. Glucagon
- E. Growth hormone
- F. Insulin
- G. Thyroid hormone

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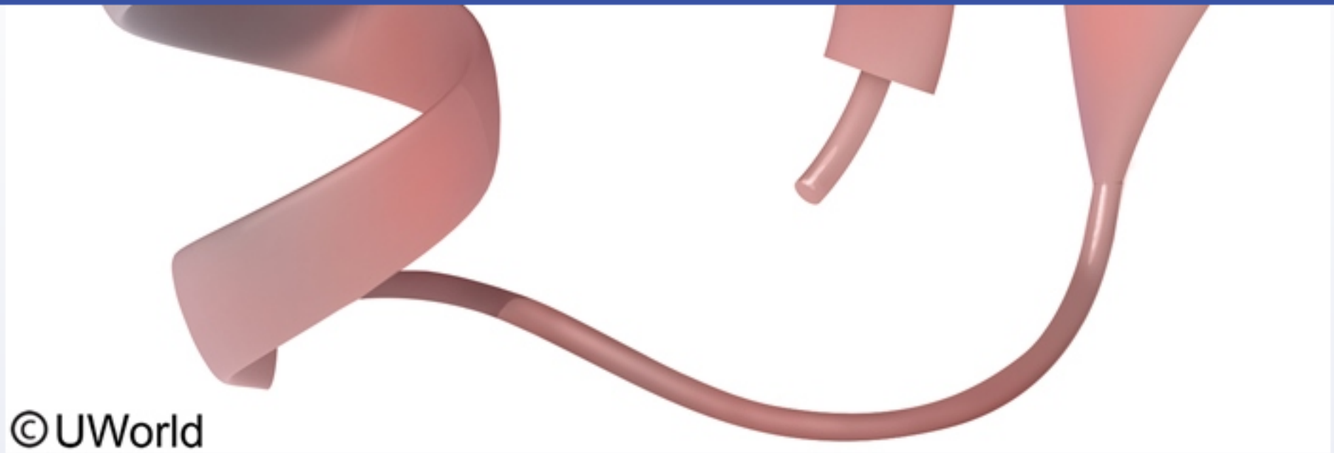

A receptor for which of the following hormones was most likely isolated in this experiment?

- A. Adrenocorticotropic hormone (11%)
- B. Antidiuretic hormone (5%)
- C. Epinephrine (5%)
- D. Glucagon (6%)
- E. Growth hormone (20%)
- F. Insulin (16%)
- ✓ G. Thyroid hormone (34%)

Omitted
Correct answer

34%
Answered correctly

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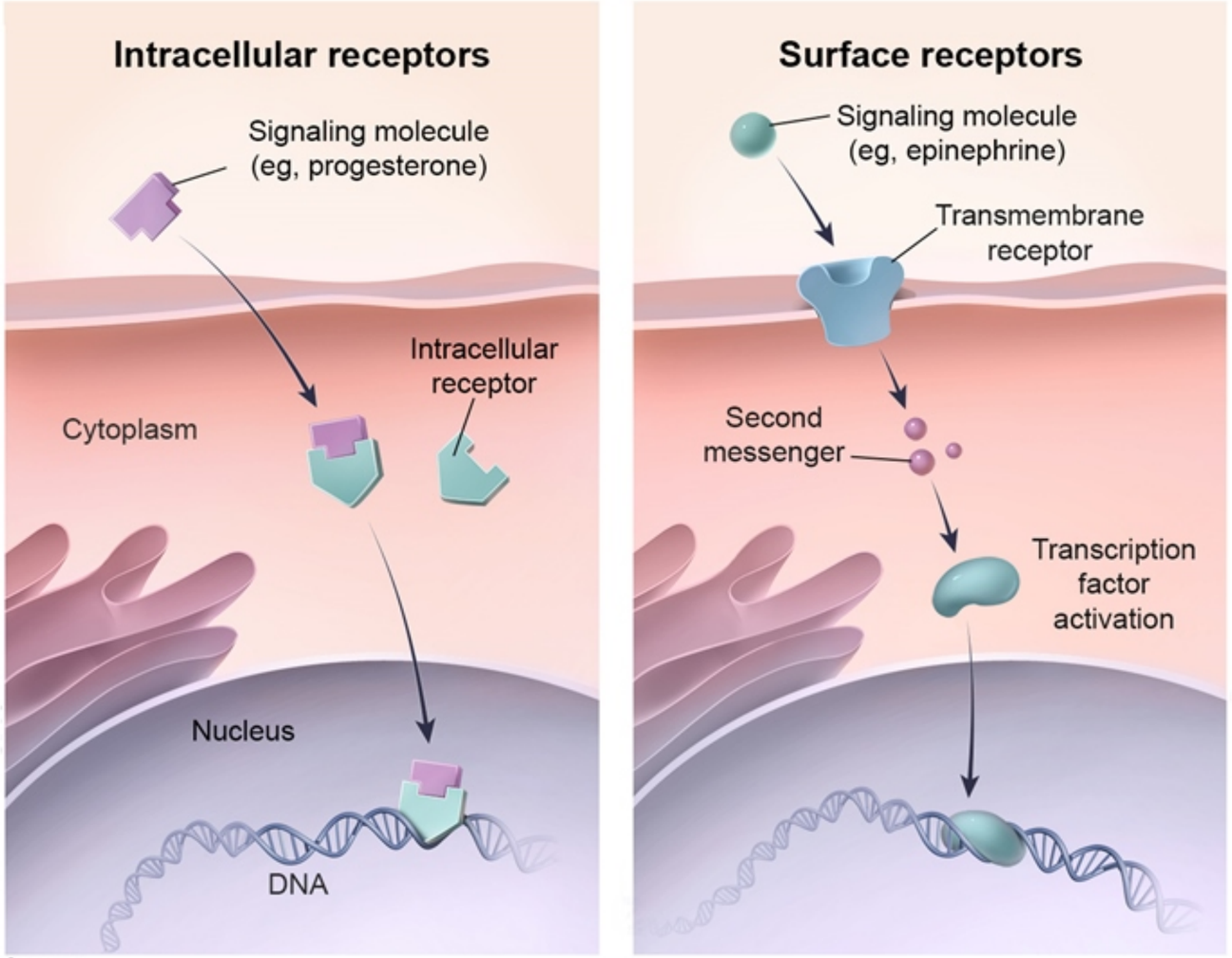

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The **zinc-finger** structure represents the most commonly identified DNA-binding domain in humans. Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine (and sometimes histidine) residues. This forms a stable, finger-shaped

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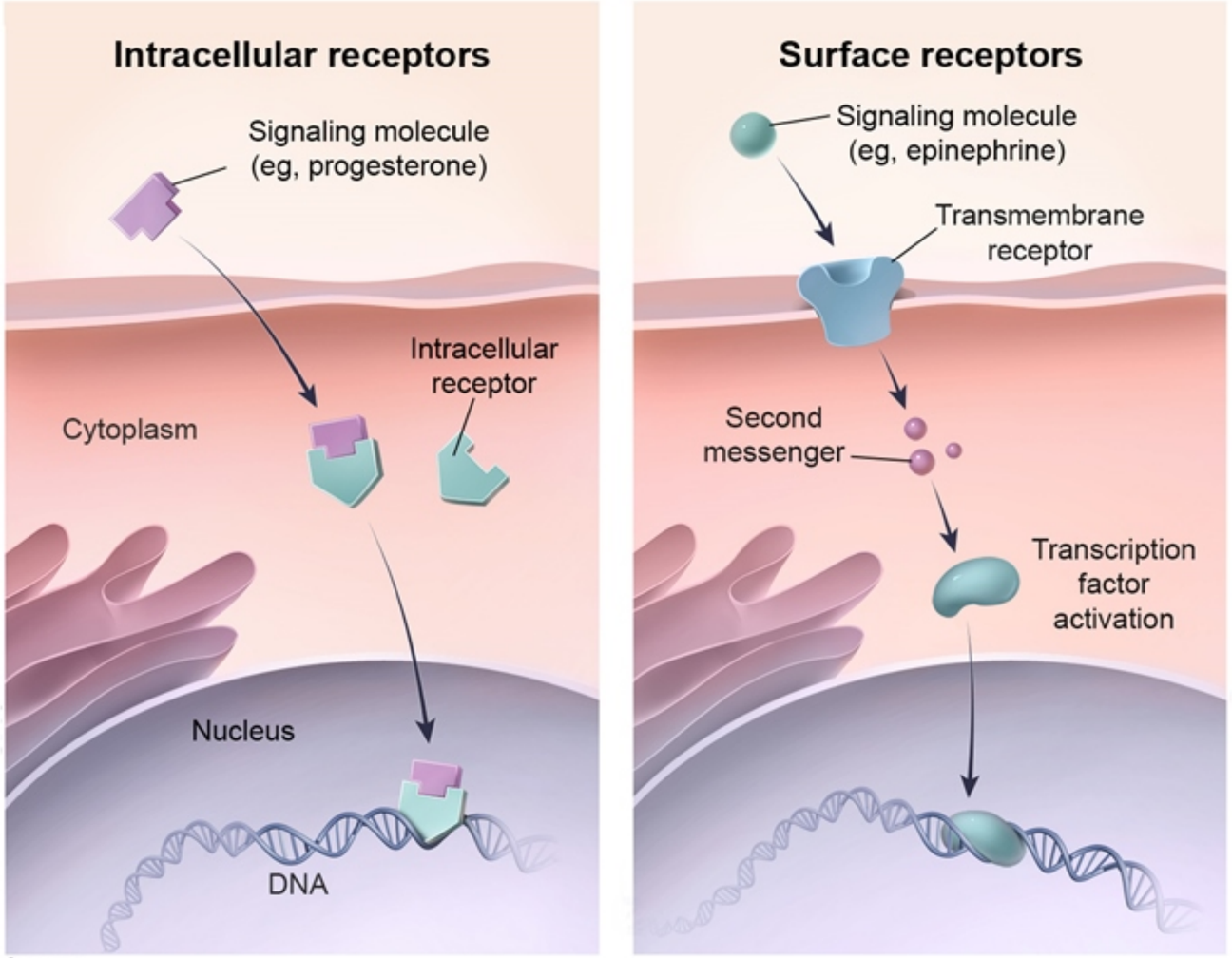

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The **zinc-finger** structure represents the most commonly identified DNA-binding domain in humans. Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine (and sometimes histidine) residues. This forms a stable, finger-shaped structure containing 2 antiparallel β- strands and an α-helix. Unique combinations of amino acids as well as the specific histidine and cysteine linkages determine DNA-binding specificity. Many transcription factors use multiple zinc-finger motifs to recognize specific genes and alter their activity.

Although most hormones alter transcription regulation to some degree in target cells, only **intracellular receptors** located in the cytoplasm or nucleus can **act directly as transcription factors**. These intracellular receptors typically bind **lipid-soluble hormones** because the ligand has to diffuse across the cell membrane to reach the receptor. Once bound to their ligand, these receptors bind directly to target DNA sequences via zinc fingers to regulate gene expression. Examples include steroid (eg, estrogen, aldosterone, cortisol), **thyroid hormone**, and fat-soluble vitamin receptors.

In contrast, non-lipid-soluble hormones interact with transmembrane receptors found on the cell membrane. These receptors use a signal transduction cascade involving second messengers with subsequent activation of non-receptor-associated transcription factors; they do not contain DNA-binding domains. Examples include the G-protein-coupled receptors that bind ACTH, ADH, epinephrine, and glucagon **(Choices A, B, C, and D)** as well as receptors with intrinsic and associated tyrosine kinase activity (eg, insulin and growth hormone receptors, respectively) **(Choices E and F)**.

Educational objective:
Zinc-finger motifs are composed of chains of amino acids bound together around a zinc atom via linkages with cysteine and histidine residues. They recognize specific DNA sequences and are used by many transcription factors to bind DNA and alter activity of target genes. Intracellular receptors that bind steroids, thyroid hormone, and fat-soluble vitamins act directly as transcription factors and contain zinc-finger binding domains.

References

- The prokaryotic zinc-finger: structure, function and comparison with the eukaryotic counterpart.

Biochemistry	Endocrine, Diabetes & Metabolism	Transcription
Subject	System	Topic

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A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

A. Galactitol to tagatose

B. Galactose to galactitol

C. Glucose to sorbitol

D. Glucose-6-phosphate to 6-phosphogluconolactone

E. Pyruvate to lactate

Submit

A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

- A. Galactitol to tagatose (0%)
- B. Galactose to galactitol (12%)
- ✓ C. Glucose to sorbitol (83%)
- D. Glucose-6-phosphate to 6-phosphogluconolactone (1%)
- E. Pyruvate to lactate (1%)

Omitted
Correct answer
C

83%
Answered correctly

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Explanation

Polyol pathway

Glucose

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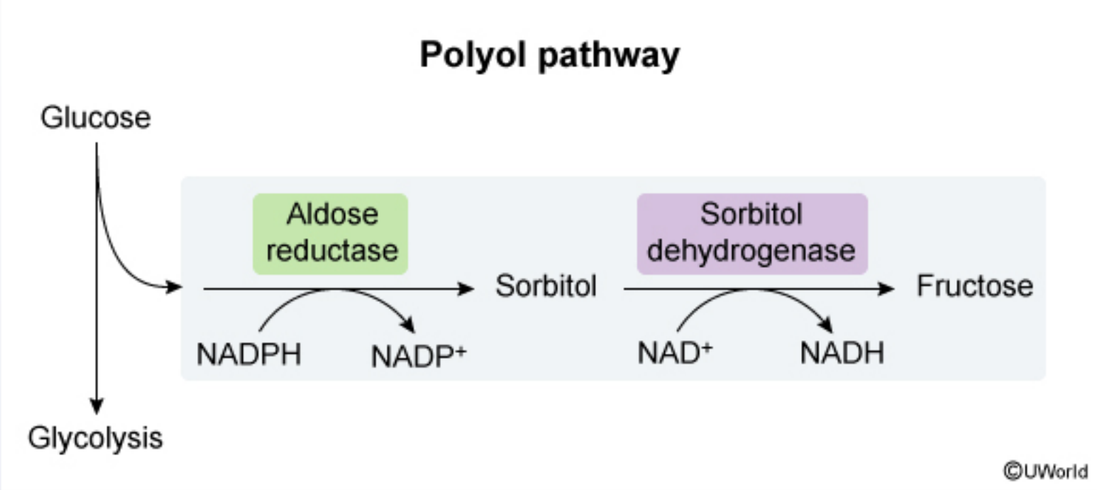

This patient has **cataracts**, an opacification of the lens of the eye that can lead to blindness, likely a result of long-standing **hyperglycemia** due to poorly controlled diabetes mellitus. Certain cells (eg, retinal, endothelial, lens, renal mesangial, Schwann) are more vulnerable to hyperglycemia-induced damage because they are unable to regulate glucose transport when circulating levels are high.

Multiple metabolic pathways are involved in the pathogenesis of hyperglycemia-induced tissue damage:

- **Advanced glycosylation end-products (AGEs):** Glucose can nonenzymatically attach to proteins and lipids, forming reversible glycosylation products that slowly stabilize into irreversible products. Under hyperglycemic conditions, AGEs accumulate and facilitate deposition of LDL in blood vessel walls and inflammatory cell invasion that causes atherosclerosis and microangiopathic complications. High glucose levels in the aqueous humor may also induce nonenzymatic glycation of lens proteins, which contributes to cataract formation.
- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

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This patient has **cataracts**, an opacification of the lens of the eye that can lead to blindness, likely a result of long-standing **hyperglycemia** due to poorly controlled diabetes mellitus. Certain cells (eg, retinal, endothelial, lens, renal mesangial, Schwann) are more vulnerable to hyperglycemia-induced damage because they are unable to regulate glucose transport when circulating levels are high.

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(Choices A and B) Aldose reductase also catalyzes the conversion of galactose (obtained from dietary lactose) to galactitol, but sorbitol dehydrogenase is incapable of oxidizing galactitol to its corresponding keto sugar (tagatose, a food sweetener). In galactosemia (galactose 1-phosphate uridyltransferase deficiency), excess galactitol is produced, which causes cataracts in newborns.

(Choice D) In the hexose monophosphate shunt, glucose-6-phosphate is converted to 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase (G6PD), generating the reducing equivalent NADPH. G6PD deficiency results in hemolytic anemia during times of increased oxidative stress.

(Choice E) Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate under anaerobic conditions. Excess lactate forms in hypoxic states, causing metabolic acidosis.

Educational objective:
In hyperglycemic states, aldose reductase converts glucose to sorbitol at a rate faster than sorbitol can be metabolized. Sorbitol accumulates in certain cells such as lens cells, causing an influx of water and resulting in osmotic cellular injury. Depletion of NADPH by aldose reductase also

- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

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Educational objective:
In hyperglycemic states, aldose reductase converts glucose to sorbitol at a rate faster than sorbitol can be metabolized. Sorbitol accumulates in certain cells such as lens cells, causing an influx of water and resulting in osmotic cellular injury. Depletion of NADPH by aldose reductase also increases oxidative stress, which accelerates development of cataracts and diabetic microvascular complications (eg, neuropathy, retinopathy).

References

- The pathobiology of diabetic complications: a unifying mechanism.

Biochemistry	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 24-year-old postpartum woman comes to the office for follow-up of gestational diabetes. The patient was diagnosed with gestational diabetes mellitus during routine screening at 28 weeks gestation; she was treated with dietary modification and exercise and required insulin briefly. Since delivery 12 weeks ago, she has continued to follow dietary recommendations, and her blood glucose has been fairly well controlled without insulin. The patient has fasting blood glucose levels of 100-120 mg/dL. Medical history is otherwise unremarkable. Family history is significant for diabetes mellitus in her mother and gestational diabetes in her sister. Vital signs are within normal limits. BMI is 22 kg/m^2. Physical examination shows no abnormalities. Her gestational diabetes and fasting hyperglycemia are suspected to be genetically predisposed. This patient's condition is most likely caused by reduced activity of which of the following enzymes?

- A. Aldolase A
- B. Enolase
- C. Glucokinase
- D. Lactate dehydrogenase
- E. Phosphofructokinase
- F. Pyruvate carboxylase
- G. Pyruvate kinase

Submit

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- A. Aldolase A (3%)
- B. Enolase (1%)
- ✓ C. Glucokinase (57%)
- D. Lactate dehydrogenase (2%)
- E. Phosphofructokinase (22%)
- F. Pyruvate carboxylase (6%)
- G. Pyruvate kinase (5%)

Omitted
Correct answer
C

57%
Answered correctly

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Explanation

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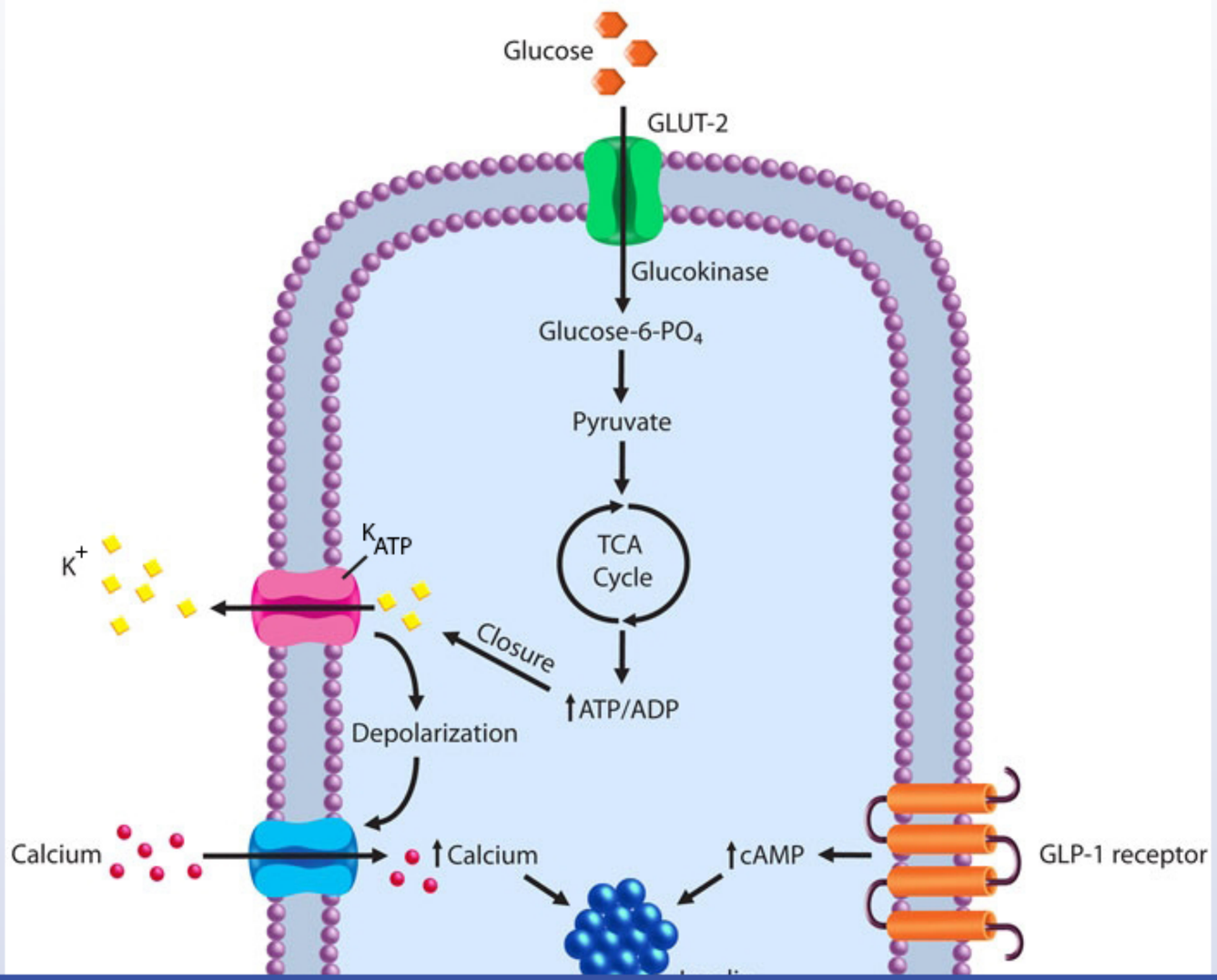
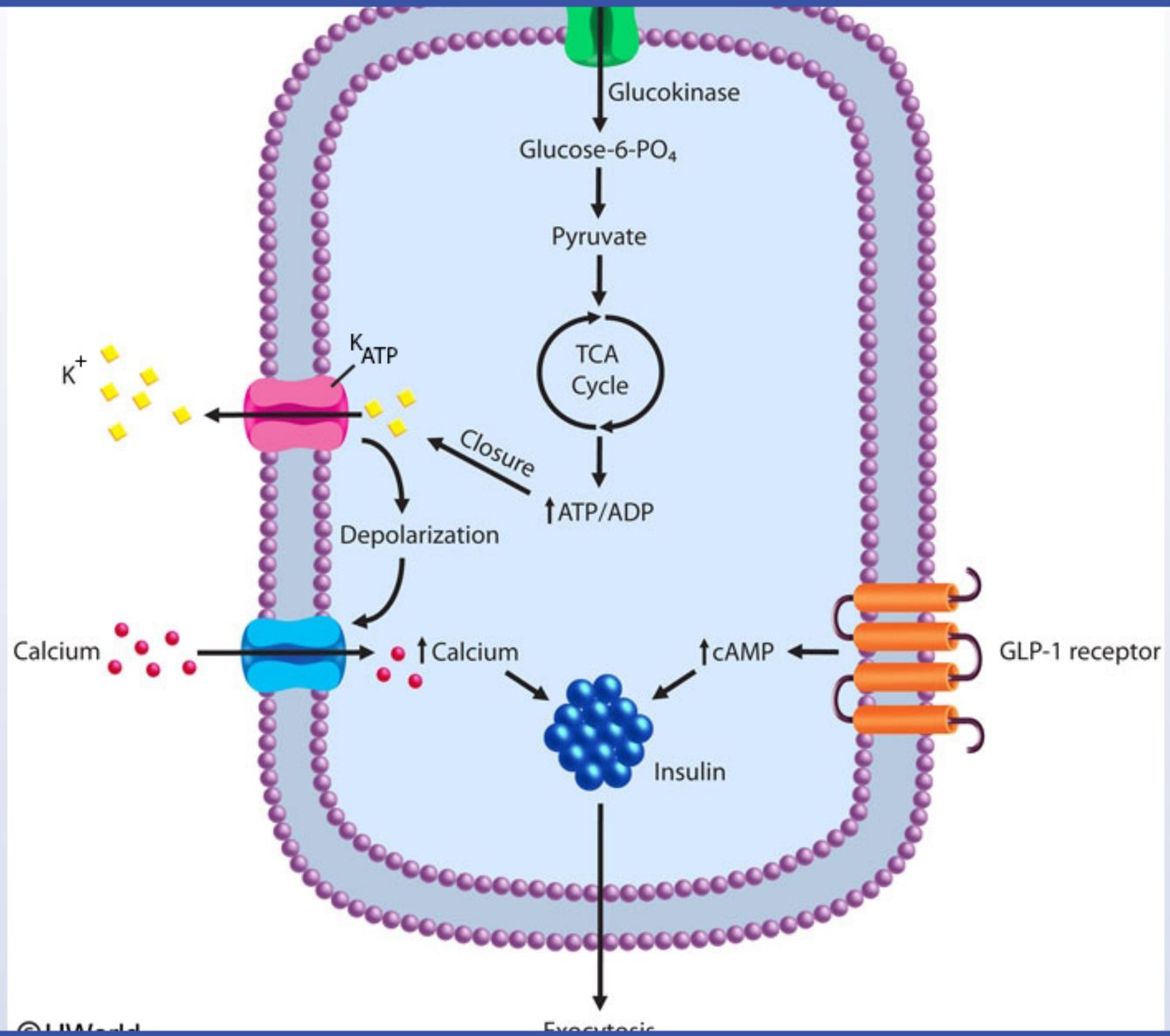
Pancreatic beta cell function




Glucokinase
Glucose-6-PO4
Pyruvate
TCA Cycle
↑ATP/ADP
Closure
K+
KATP
Depolarization
Calcium
↑Calcium
↑cAMP
GLP-1 receptor
Insulin
Exocytosis

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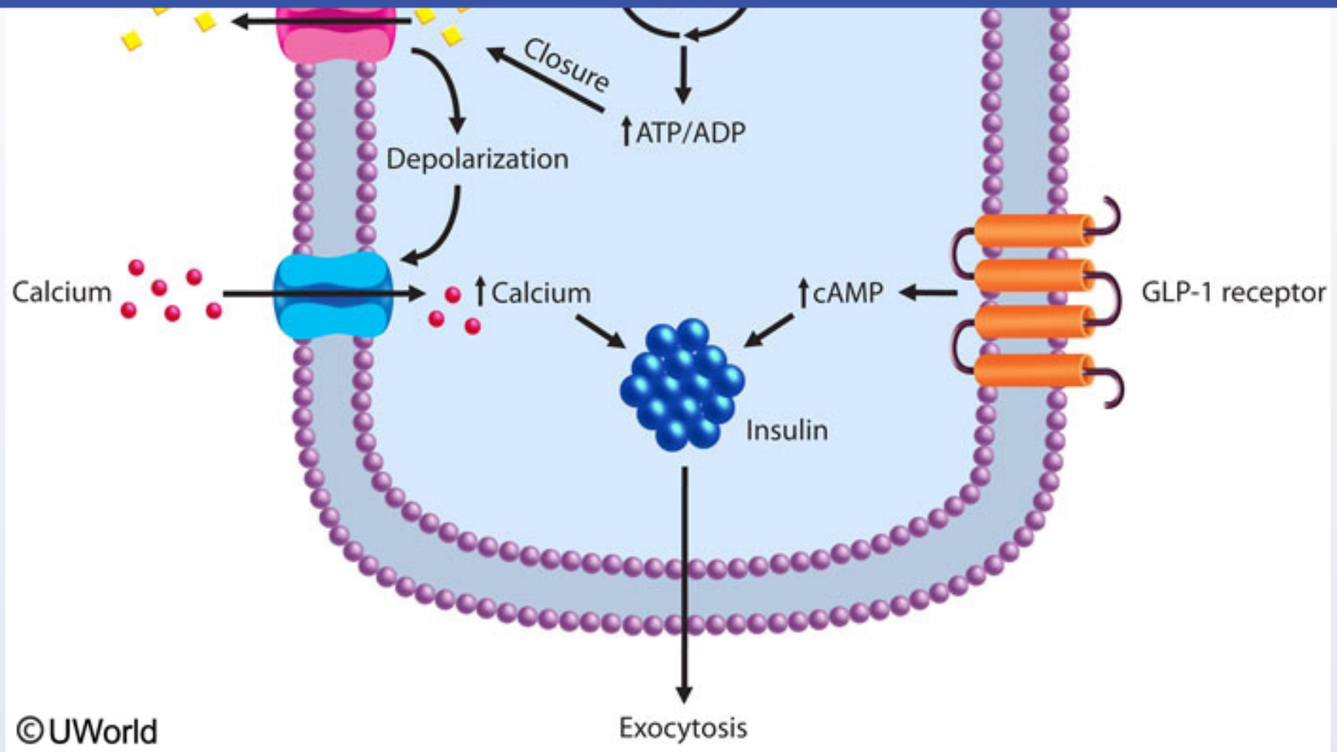

Glucose-induced insulin release from pancreatic beta cells requires the following steps:

1. Glucose enters the beta cell through glucose transporter type 2 (GLUT-2).
2. Glucose is metabolized by glucokinase to glucose-6-phosphate.
3. Glucose-6-phosphate enters glycolysis to produce ATP.
4. Increased ATP levels causes closure of ATP-sensitive potassium (K_{ATP}) channels.
5. Depolarization of beta cells triggers opening of voltage-dependent calcium channels.
6. Influx of calcium causes insulin release.

Glucokinase has a lower glucose affinity than other hexokinases, which allows it to limit the rate of glucose entry into the glycolytic pathway based on blood glucose levels. It therefore functions as a **glucose sensor** for beta cells in controlling insulin release.

6. Influx of calcium causes insulin release.

Glucokinase has a lower glucose affinity than other hexokinases, which allows it to limit the rate of glucose entry into the glycolytic pathway based on blood glucose levels. It therefore functions as a **glucose sensor** for beta cells in controlling insulin release.

Heterozygous mutations of the glucokinase gene that decrease the activity or affinity of the enzyme cause a decrease in beta cell glucose metabolism, leading to reduced ATP formation and insulin secretion at any given glucose level. Glucokinase mutations are one cause of **maturity-onset diabetes of the young (MODY)**, an autosomal dominant disorder characterized by **mild hyperglycemia** that often worsens with pregnancy-induced insulin resistance. In contrast to those with more common type 2 diabetes mellitus, patients with MODY are typically younger and nonobese, and the condition is **nonprogressive**, even without treatment.

(Choices A, B, E, and G) Glycolytic enzyme deficiencies (eg, aldolase A, enolase, phosphofructokinase, pyruvate kinase) generally present with hemolytic anemia because red blood cells rely completely on anaerobic glycolysis for energy production.

(Choice D) Lactate dehydrogenase is present in most cells and catalyzes the conversion of pyruvate to lactate during anaerobic glycolysis. Deficiency can cause decreased exercise tolerance and muscle stiffness.

(Choice F) Pyruvate carboxylase, one of the gluconeogenesis pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

Educational objective:
Insulin release by pancreatic beta cells is stimulated by increased glucose metabolism and ATP production. Glucokinase functions as a glucose sensor in pancreatic beta cells by controlling the rate of glucose entry into the glycolytic pathway. Mutations in the glucokinase gene lead to a state in which higher glucose levels are required to stimulate insulin secretion and are a cause of maturity-onset diabetes of the young.

References

- Glucokinase MODY and implications for treatment goals of common forms of diabetes.

Biochemistry	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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A 31-year-old previously healthy man comes to the office due to myalgias, anorexia, and skin rash. He does not use tobacco, alcohol, or illicit drugs. The patient works as a personal trainer and is a bodybuilding enthusiast. He denies using anabolic steroids but has been consuming large amounts of raw egg whites for the past several months. Physical examination shows macular dermatitis of the extremities. A water-soluble vitamin deficiency is suspected as the cause of his condition. Which of the following biochemical conversions most likely uses the deficient vitamin as a cofactor?

A. Glucose to ribose-5-phosphate

B. Pyruvate to acetyl-CoA

C. Pyruvate to alanine

D. Pyruvate to oxaloacetate

E. Succinate to oxaloacetate

Submit

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- A. Glucose to ribose-5-phosphate (6%)
- B. Pyruvate to acetyl-CoA (24%)
- C. Pyruvate to alanine (8%)
- ✓ D. Pyruvate to oxaloacetate (50%)
- E. Succinate to oxaloacetate (9%)

Omitted
Correct answer
D

50%
Answered correctly

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Time Spent

03/31/2020
Last Updated

Explanation

Biotin (vitamin B_7) as a cofactor	
Enzyme	**Reaction**

Explanation

Biotin (vitamin B_7) as a cofactor	
Enzyme	**Reaction**
Pyruvate carboxylase	Pyruvate to oxaloacetate (gluconeogenesis)
Acetyl-CoA carboxylase	Acetyl-CoA to malonyl-CoA (fatty acid synthesis)
Propionyl-CoA carboxylase	Propionyl-CoA to methylmalonyl-CoA (fatty acid oxidation)

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Biotin (vitamin B_7) is an important cofactor for several **carboxylase** enzymes. It functions as a CO_2 carrier and plays an essential role in carbohydrate, lipid, and amino acid metabolism. In the liver, the conversion of **pyruvate to oxaloacetate** for gluconeogenesis requires pyruvate carboxylase and biotin.

Biotin deficiency is rare but can occur secondary to poor diet, excessive raw egg white consumption (due to high levels of **biotin-binding avidin** in egg whites), and congenital disorders of biotin metabolism. Patients with biotin deficiency present with nonspecific symptoms, including changes in mental status, myalgias, anorexia, and chronic **dermatologic changes** such as macular dermatitis. Biotin-deficient individuals can also develop **metabolic acidosis** as a result of increased conversion of pyruvate to lactic acid.

(Choice A) Niacin (vitamin B_3), in the form of $NADP^+$, is used to oxidize glucose-6-phosphate in the pentose phosphate pathway, generating ribose-5-phosphate and NADPH in the process.

(Choice B) Thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), and lipoic acid are the 5 cofactors

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(Choice C) Pyridoxal phosphate (vitamin B_6) acts as a cofactor for alanine transaminase, which catalyzes the reversible reaction between pyruvate and glutamate to alanine and alpha-ketoglutarate in the liver and muscle tissue.

(Choice E) Production of oxaloacetate from succinate in the TCA cycle requires 2 enzymes (succinate dehydrogenase and malate dehydrogenase), along with riboflavin (vitamin B_2) and niacin (vitamin B_3) in the forms of cofactors FAD^+ and NAD^+, respectively.

Educational objective:
Biotin acts as a CO_2 carrier on the surface of carboxylase enzymes and is an essential cofactor for numerous reactions, including the conversion of pyruvate to oxaloacetate and fatty acid metabolism. Excess ingestion of avidin, found in egg whites, has been associated with biotin deficiency. This condition presents with mental status changes, myalgias, anorexia, macular dermatitis, and lactic acidosis.

Biochemistry	Endocrine, Diabetes & Metabolism	Tca cycle
Subject	System	Topic

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Biochemistry	Endocrine, Diabetes & Metabolism	Tca cycle
Subject	System	Topic

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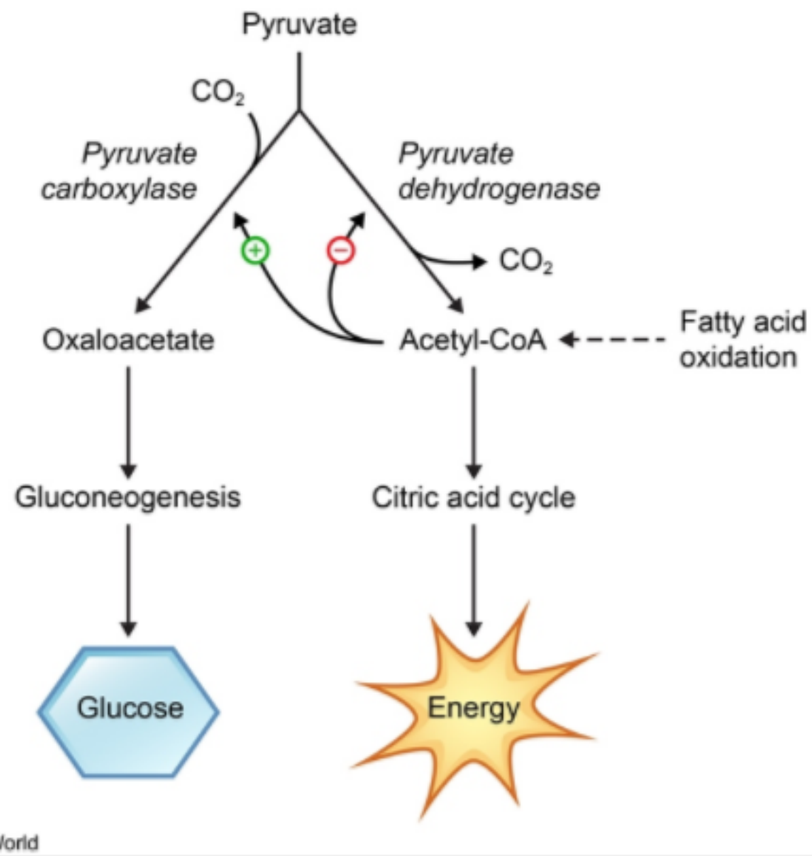
carbohydrate, lipid, and amino acid metabolism. In the liver, the conversion of **pyruvate to oxaloacetate** for gluconeogenesis requires pyruvate

Exhibit Display

Metabolic fate of pyruvate



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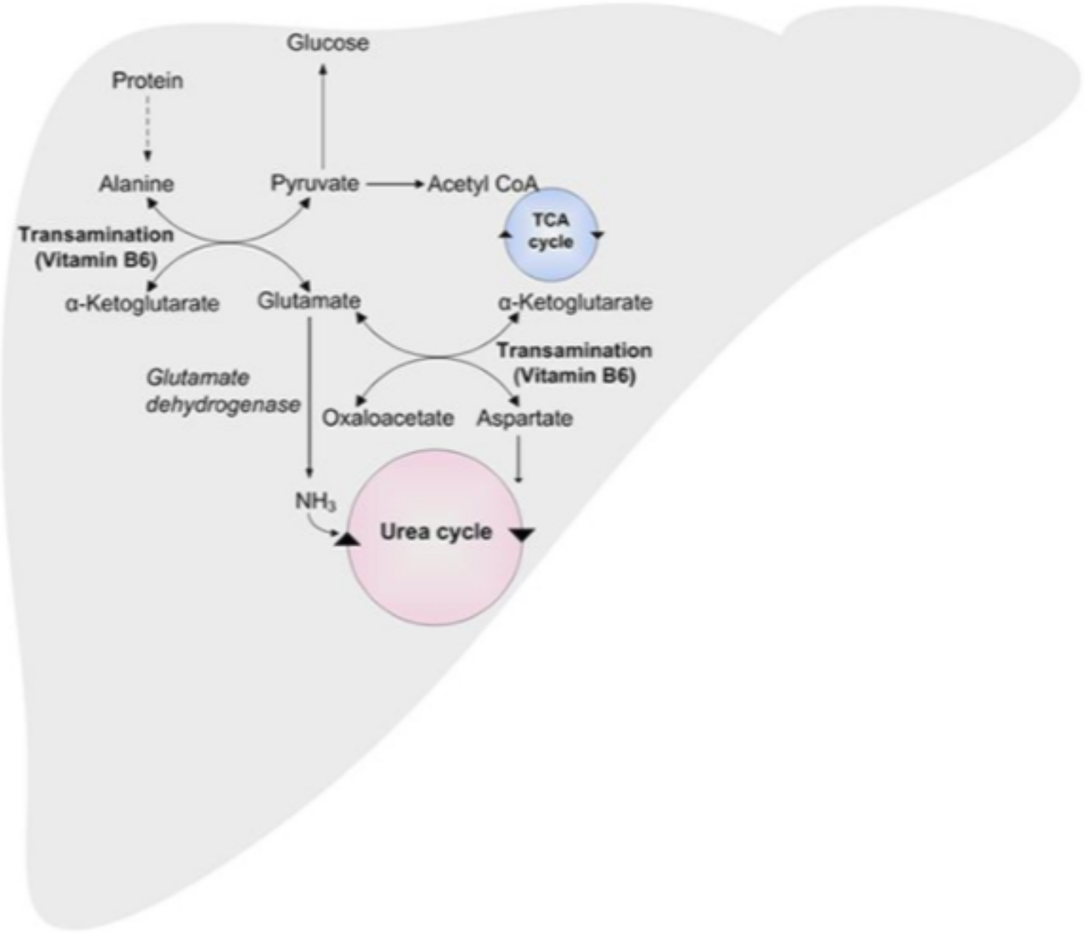

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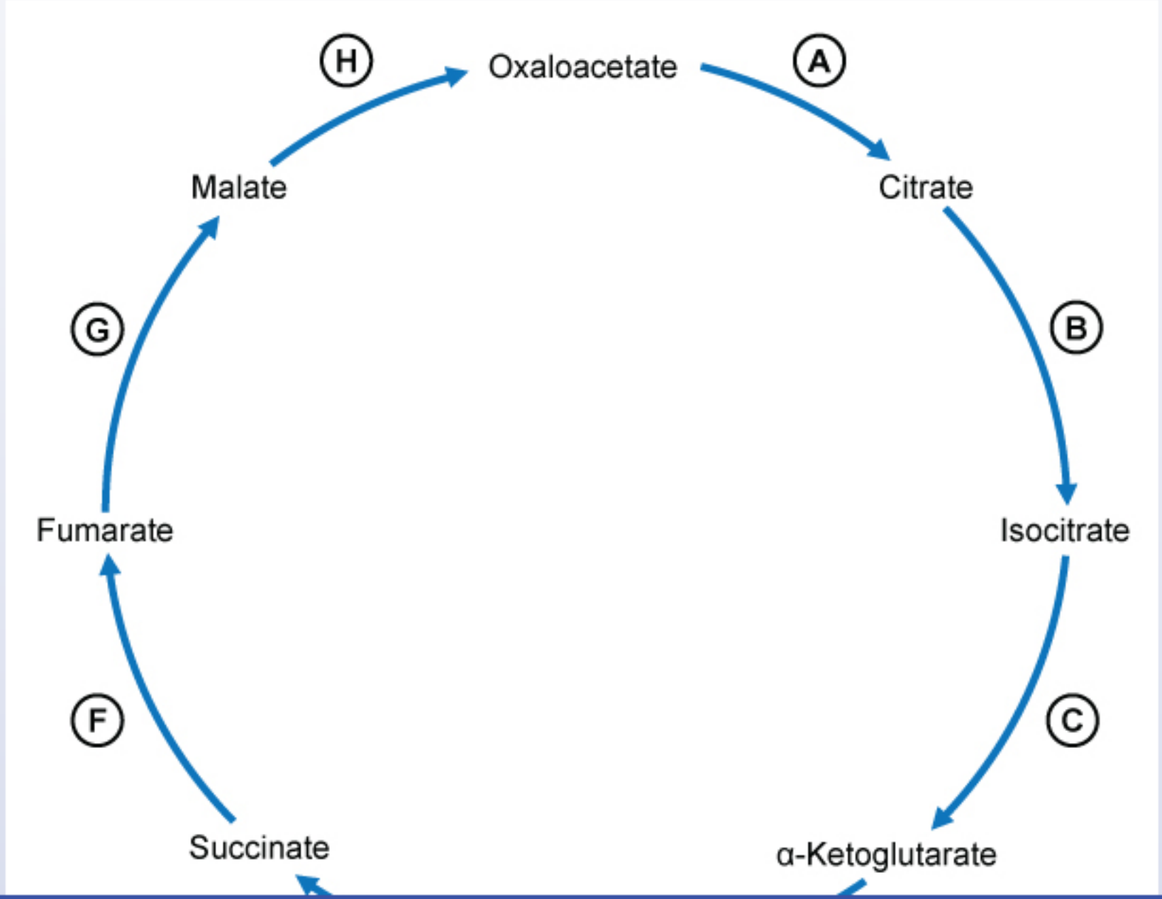
A 43-year-old man prospecting for gold in Arizona becomes stuck in the desert after his truck breaks down. He brought a large supply of water with him but only a few granola bars as food. After 3 days, he is able to flag down a passing vehicle and obtain transportation to the nearest settlement. During this ordeal, his liver begins to synthesize large quantities of glucose from source molecules such as alanine, lactate, and glycerol. As part of this process, phosphoenolpyruvate is formed from oxaloacetate in a reaction that requires a specific nucleoside triphosphate as a cofactor. Which of the following reactions directly synthesizes this cofactor?



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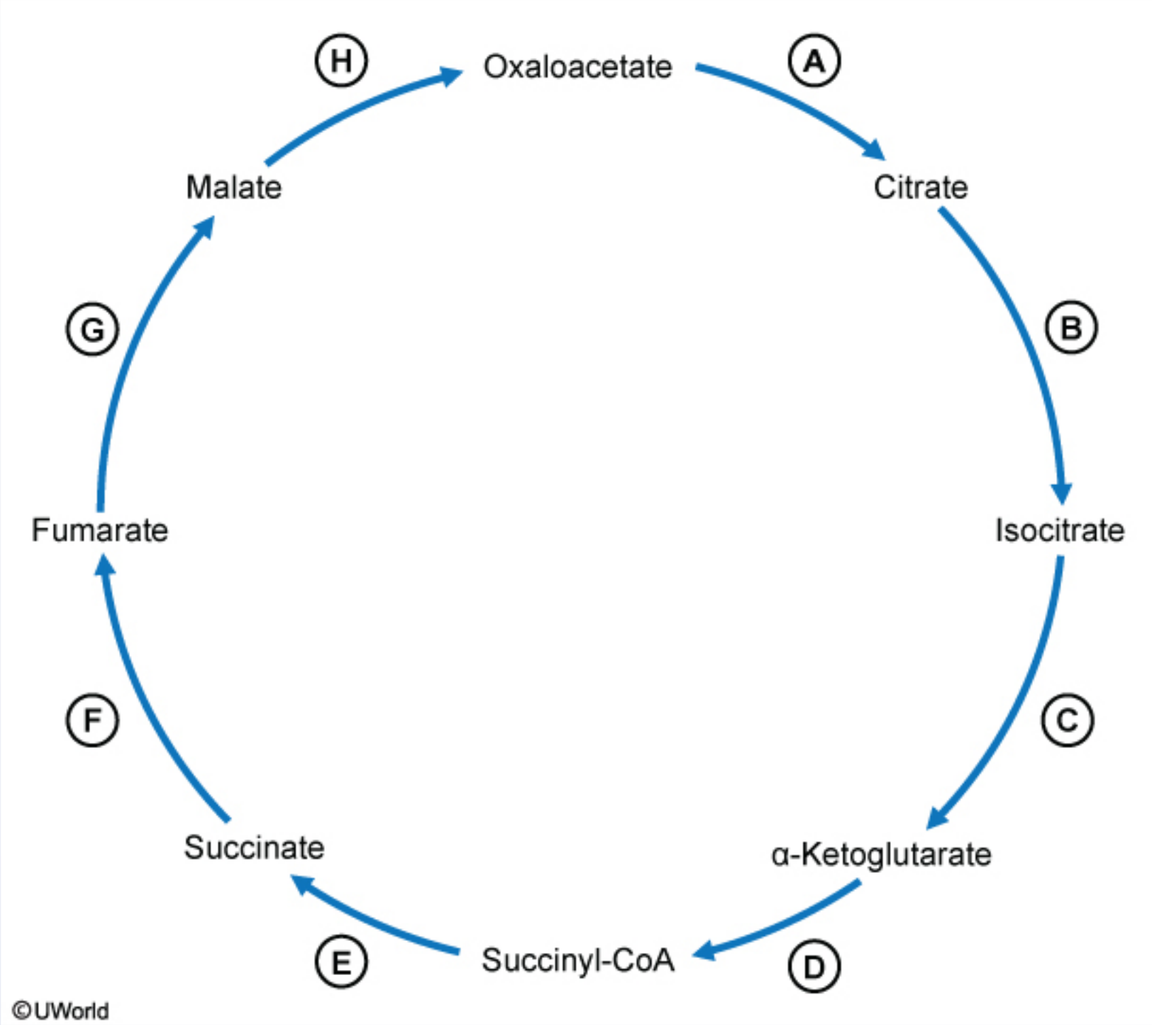

A. A

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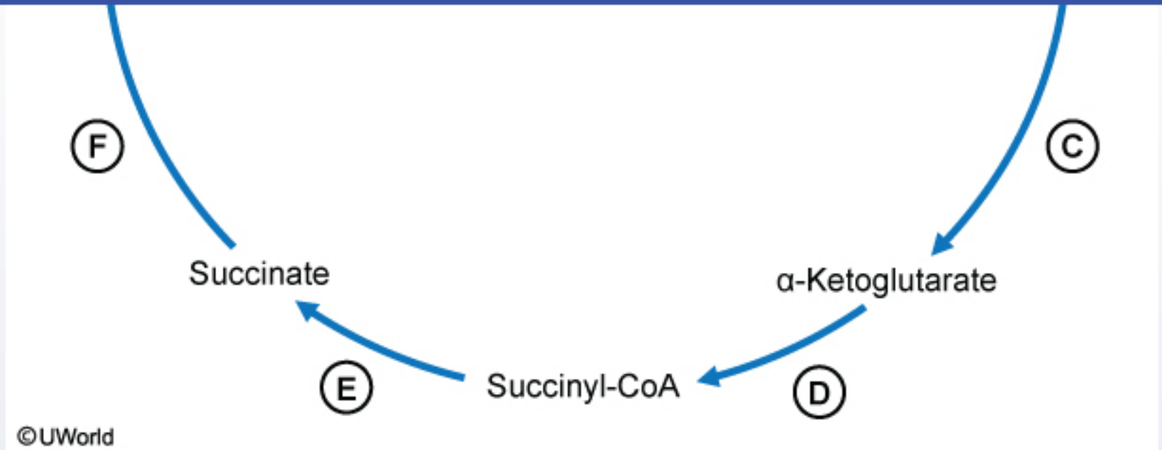

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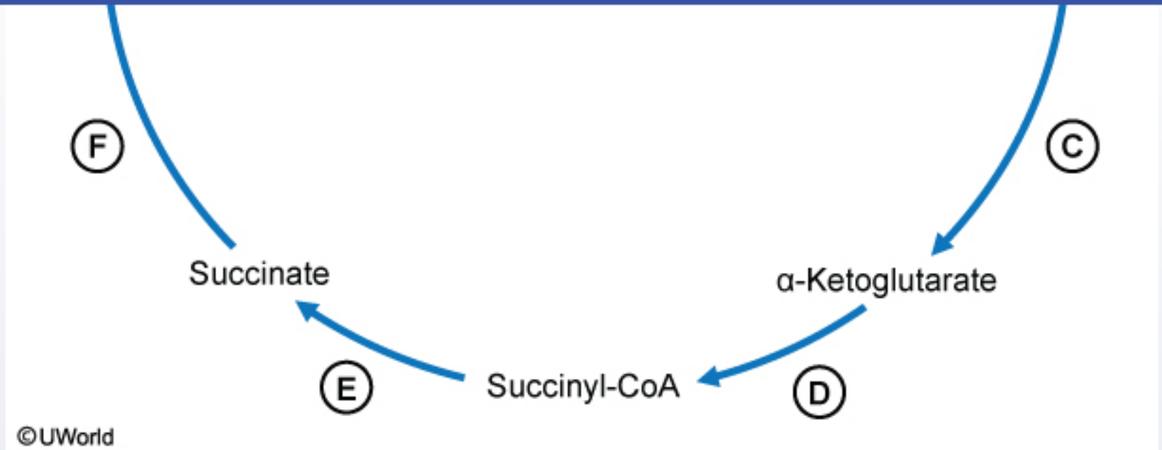

A. A (3%)
B. B (3%)
C. C (10%)
D. D (20%)
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G. G (4%)
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Correct answer

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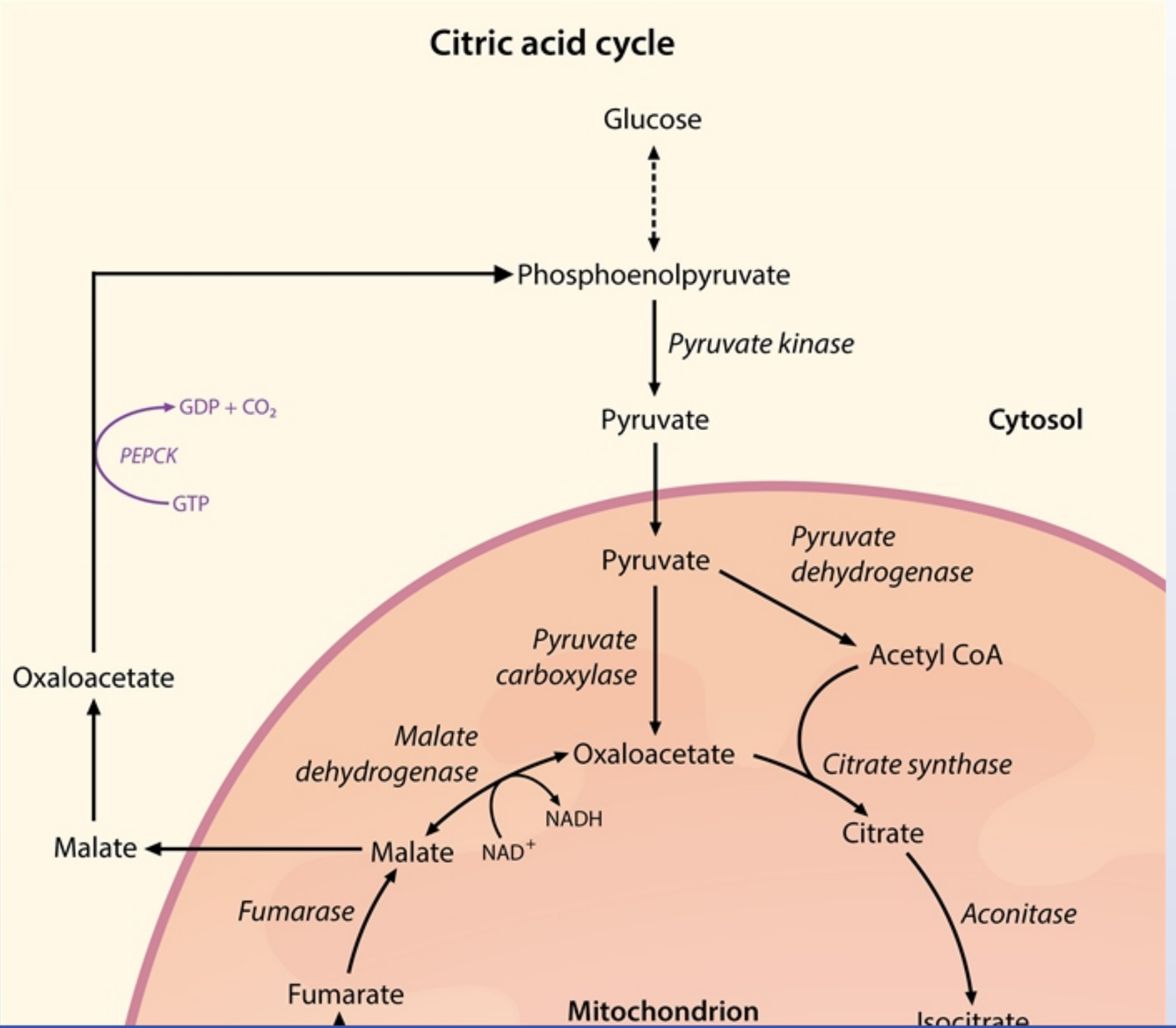

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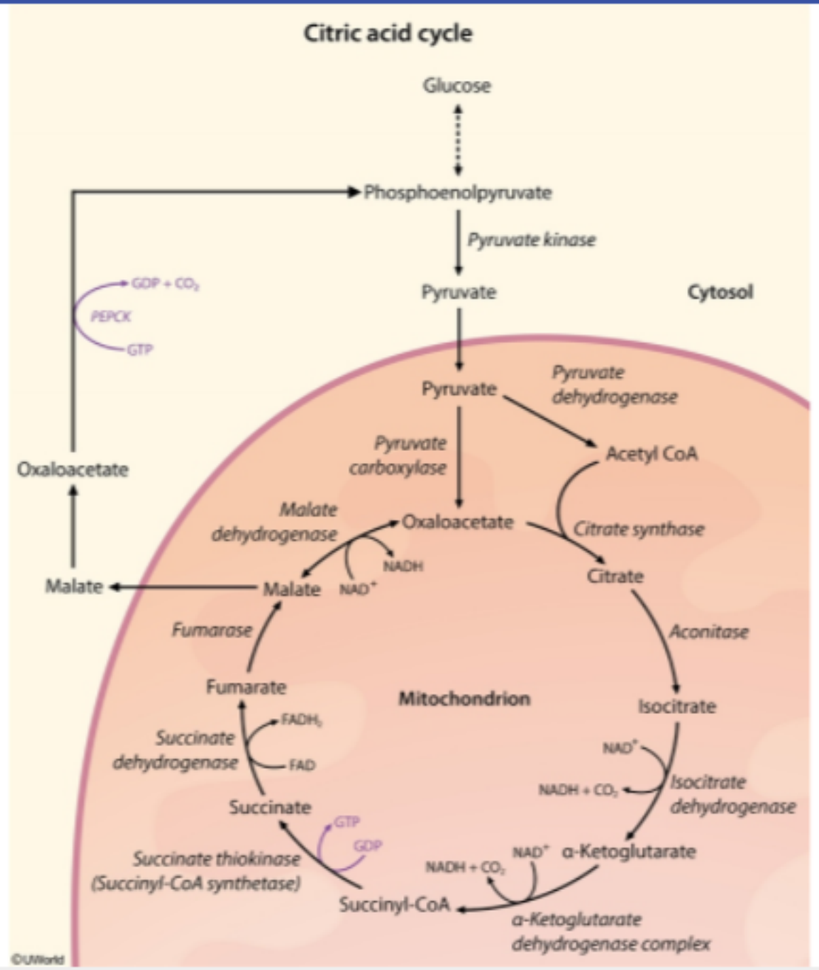

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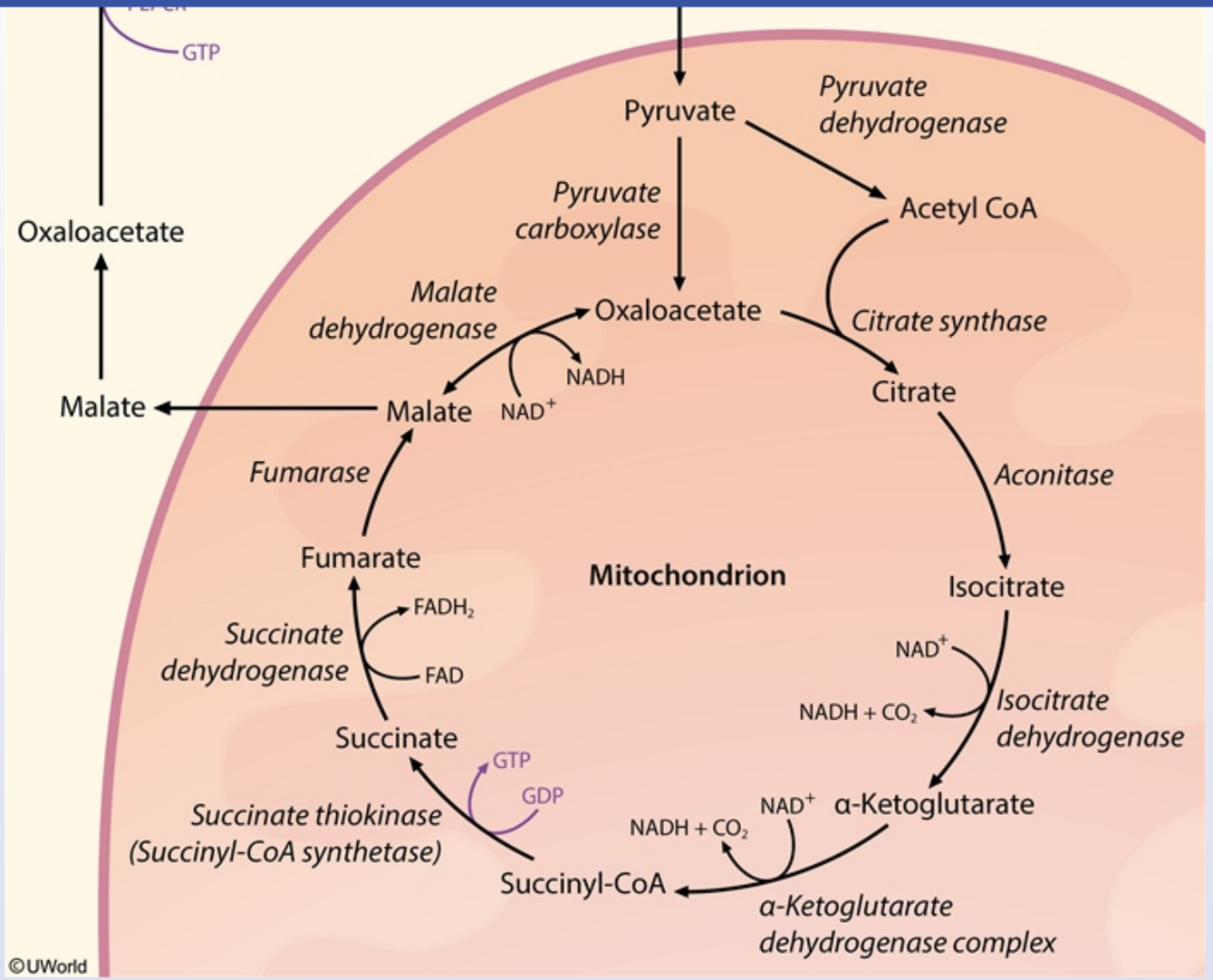
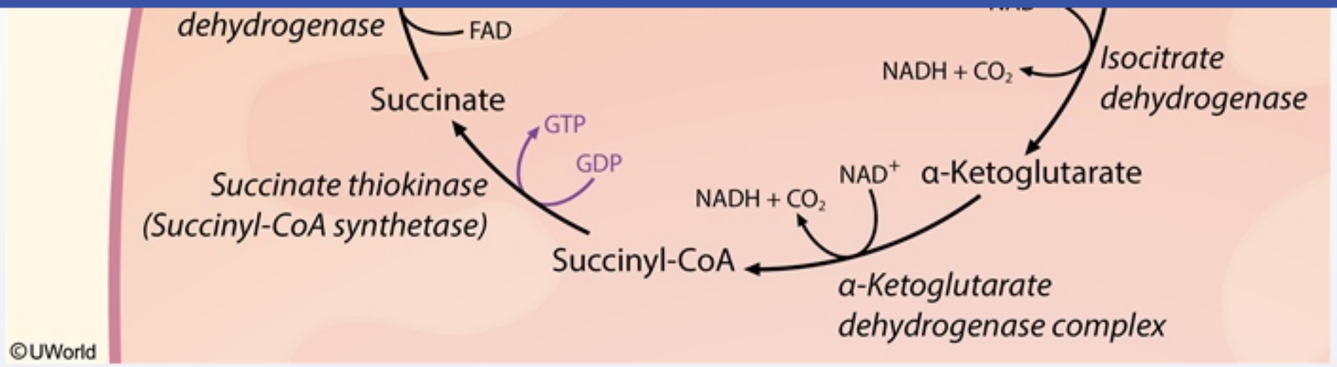


The majority of ATP used for cellular processes is generated by the oxidation of acetate in the tricarboxylic acid (TCA) cycle. The enzymes of the TCA cycle are located in the mitochondria and generate reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide



The majority of ATP used for cellular processes is generated by the oxidation of acetate in the tricarboxylic acid (TCA) cycle. The enzymes of the TCA cycle are located in the mitochondria and generate reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) **(Choices C, D, F, and H)**. These molecules drive the process of oxidative phosphorylation, which converts their reducing potential into high-energy ATP via the electron transport chain.

ATP can also be generated by **substrate-level phosphorylation**, which involves the direct transfer of a phosphate group from a reactive intermediate to a nucleotide diphosphate (eg, ADP, GDP). **Succinyl-CoA synthetase** converts succinyl-CoA to succinate and uses the high-energy thioester present in succinyl-CoA to drive **GTP synthesis**. This GTP can then be used to transphosphorylate ADP to ATP, or it may be utilized by specific GTP-hydrolyzing enzymes, such as **phosphoenolpyruvate carboxykinase** (converts oxaloacetate to phosphoenolpyruvate during gluconeogenesis).

Educational objective:
GTP is synthesized by succinyl-CoA synthetase during the conversion of succinyl-CoA to succinate in the citric acid cycle. During gluconeogenesis, phosphoenolpyruvate carboxykinase uses GTP to synthesize phosphoenolpyruvate from oxaloacetate.

Biochemistry	Endocrine, Diabetes & Metabolism	Tca cycle
Subject	System	Topic

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A 36-year-old man comes to the office due to skin lesions on his palms. The patient has yellowish skin nodules over the palmar creases that have been increasing in size and number over the past several years. He also has small clusters of yellow papules on his elbows, knees, and buttocks. His father died of a myocardial infarction at age 56. Biopsy of his lesions shows accumulation of lipid-laden macrophages. Immunoblot analysis suggests a lack of ApoE3 and ApoE4 in his circulating lipoproteins. Which of the following is most likely impaired in this patient?

A. ApoC-2 production

B. Cholesterol esterification in the blood

C. Chylomicron remnant uptake by liver cells

D. LDL particle uptake by hepatocytes

E. Lipoprotein lipase activity

Submit

A 36-year-old man comes to the office due to skin lesions on his palms. The patient has yellowish skin nodules over the palmar creases that have been increasing in size and number over the past several years. He also has small clusters of yellow papules on his elbows, knees, and buttocks. His father died of a myocardial infarction at age 56. Biopsy of his lesions shows accumulation of lipid-laden macrophages. Immunoblot analysis suggests a lack of ApoE3 and ApoE4 in his circulating lipoproteins. Which of the following is most likely impaired in this patient?

- A. ApoC-2 production (1%)
- B. Cholesterol esterification in the blood (7%)
- ✓ C. Chylomicron remnant uptake by liver cells (41%)
- D. LDL particle uptake by hepatocytes (35%)
- E. Lipoprotein lipase activity (13%)

Omitted
Correct answer
C

41%
Answered correctly

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Explanation

Important inherited hyperlipoproteinemias			
Dyslipidemia	**Protein defect**	**Elevated lipoproteins**	**Major manifestations**

Important inherited hyperlipoproteinemias			
Dyslipidemia	**Protein defect**	**Elevated lipoproteins**	**Major manifestations**
Familial chylomicronemia syndrome (type I)	• Lipoprotein lipase • ApoC-2	Chylomicrons	• **Acute pancreatitis** • Lipemia retinalis • Eruptive xanthomas
Familial hypercholesterolemia (type II A)	• LDL receptor • ApoB-100	**LDL**	• **Premature atherosclerosis** • Tendon xanthomas • Xanthelasmas
Familial dysbetalipoproteinemia (type III)	• ApoE	Chylomicron & VLDL remnants	• **Premature atherosclerosis** • Tuboeruptive & palmar xanthomas
Familial hypertriglyceridemia (type IV)	• Polygenic	VLDL	• Associated with coronary disease, pancreatitis & diabetes

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Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is characterized by xanthomas and premature coronary and peripheral vascular

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Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is characterized by xanthomas and premature coronary and peripheral vascular disease. It is an autosomal recessive disorder that is clinically more severe in patients with other conditions affecting lipoprotein metabolism (eg, diabetes, hypothyroidism).

The primary defects in familial dysbetalipoproteinemia are in **ApoE3 and ApoE4**, apolipoproteins found on the triglyceride-rich lipoproteins (**chylomicrons and VLDLs**) that are responsible for binding hepatic apolipoprotein receptors. Without ApoE3 and ApoE4, the liver cannot efficiently remove chylomicrons and VLDL remnants from the circulation, causing their accumulation in the blood and resultant elevations in **cholesterol and triglyceride** levels.

(Choices A and E) Familial chylomicronemia syndrome is an autosomal recessive disorder characterized by defective lipoprotein lipase activity with increased synthesis and decreased clearance of chylomicron particles (and VLDL to a lesser extent). It can also be due to ApoC2 deficiency because lipoprotein lipase is activated by ApoC2 on chylomicrons and VLDL.

(Choice B) ApoA1 is required for esterification of free cholesterol in HDL particles by lecithin-cholesterol acyltransferase (LCAT). ApoA1 and LCAT deficiencies result in low HDL levels and increased circulating free cholesterol levels.

(Choice D) Familial hypercholesterolemia is associated with increased levels of LDL cholesterol. It is caused by defects in the ApoB/E LDL receptor or ApoB-100 ligand, leading to decreased hepatic clearance of LDL.

Educational objective:
Familial dysbetalipoproteinemia (type III hyperlipoproteinemia) is an autosomal recessive disorder characterized by elevated cholesterol and triglyceride levels. It is caused by defects in ApoE3 and ApoE4, leading to decreased clearance of chylomicrons and VLDL remnants. Patients can develop eruptive and palmar xanthomas and premature atherosclerosis.

Biochemistry	Endocrine, Diabetes & Metabolism	Dyslipidemia
Subject	System	Topic

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An 18-month-old boy is being evaluated for neurologic regression. He had a normal neonatal course and early development until age 5 months. The boy subsequently developed a gradual regression of developmental milestones such as the inability to sit with support, poor head control, and loss of a social smile. His weight and height are below the fifth percentile. On physical examination, he has an enlarged liver and spleen, diminished deep tendon reflexes in all limbs, and hypotonia. Funduscopic findings are shown in the exhibit. This patient most likely has an accumulation of which substrate?

A. Cerebroside sulfate
B. Galactocerebroside
C. Globotriaosylceramide
D. Glucocerebroside
E. GM2 ganglioside
F. Sphingomyelin

Submit

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- A. Cerebroside sulfate (1%)
- B. Galactocerebroside (9%)
- C. Globotriaosylceramide (0%)
- D. Glucocerebroside (8%)
- E. GM2 ganglioside (20%)
- ✓ F. Sphingomyelin (59%)

Omitted
Correct answer
F

59%
Answered correctly

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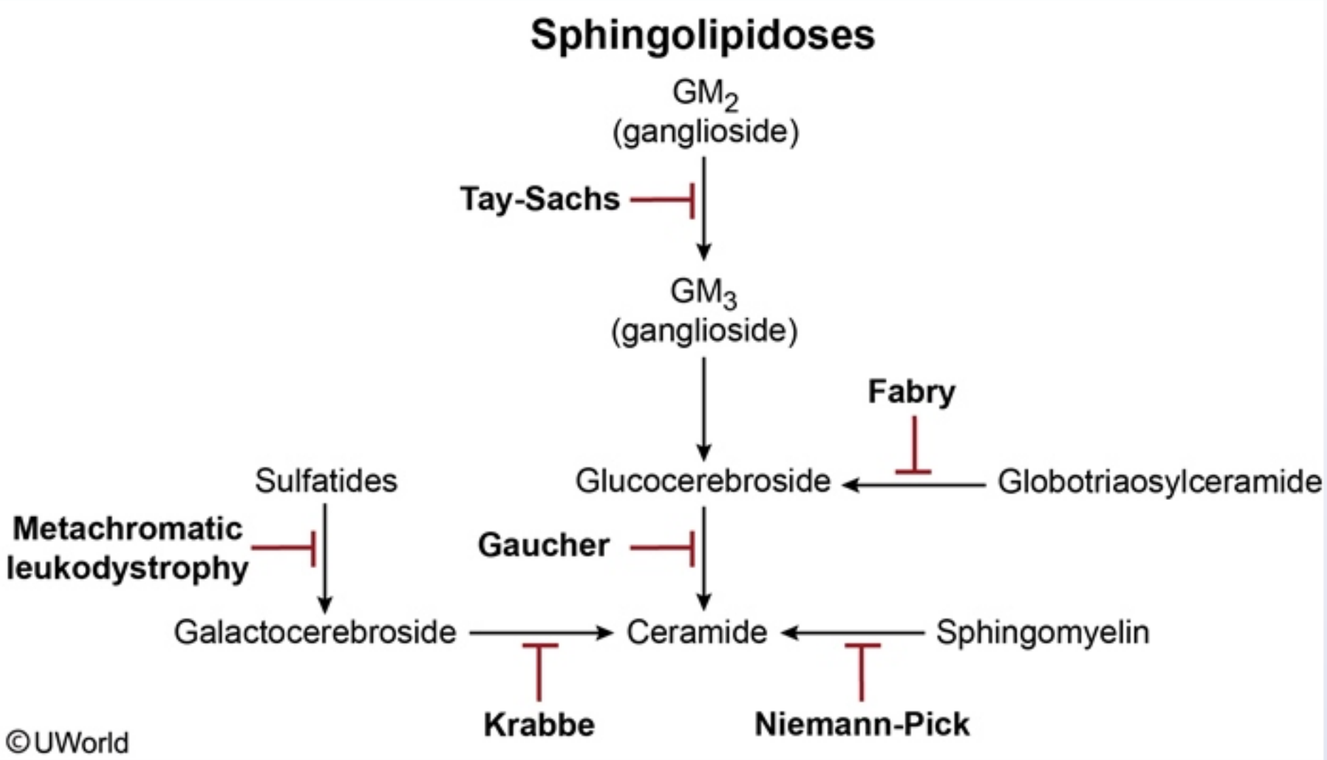
Time Spent

01/27/2020
Last Updated

Explanation

Sphingolipidoses

GM_2



Niemann-Pick disease is an autosomal recessive disorder common among Ashkenazi Jews and is characterized by **sphingomyelinase deficiency**. Sphingomyelinase is responsible for the breakdown of sphingomyelin, a lipid constituent of cell membranes. In Niemann-Pick disease, **sphingomyelin accumulation** within lysosomes results in cells that appear enlarged, foamy, and vacuolated on electron microscopy. These lipid-laden foam cells (black arrows) accumulate in the liver and spleen and cause **hepatosplenomegaly**. Progressive neuronal accumulation is responsible for **hypotonia** and **neurologic degeneration** (eg, failure to progress developmentally, loss of milestones). Retinal accumulation leads to a cherry-red macular spot (blue arrow). This patient presents with the classic infantile type A variant that results in hepatosplenomegaly, progressive neurologic deterioration, and death by age 3 years.

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(Choice A) In patients with metachromatic leukodystrophy, central nervous system accumulation of cerebroside sulfate is caused by arylsulfatase A deficiency. Central and peripheral demyelination leads to peripheral neuropathy and ataxia.

(Choice B) In Krabbe disease, galactocerebrosidase deficiency causes accumulation of galactocerebroside and psychosine. Infants have developmental delay and/or regression, hypotonia, optic atrophy, and seizures.

(Choice C) In Fabry disease, α-galactosidase A deficiency causes globotriaosylceramide (ceramide trihexoside) accumulation. Clinical manifestations begin in childhood with neuropathic pain and dermatologic pathology (eg, telangiectasias, angiokeratomas).

(Choice D) Glucocerebroside accumulation occurs in Gaucher disease, an autosomal recessive disorder of β-glucocerebrosidase deficiency. Patients typically have hepatosplenomegaly, pancytopenia, and skeletal problems.

(Choice E) Patients with Tay-Sachs disease are deficient in β-hexosaminidase A, which leads to GM2 accumulation in neurons. Neurologic regression and cherry-red macular spots are classic symptoms (similar to Niemann-Pick disease), but hepatosplenomegaly is absent.

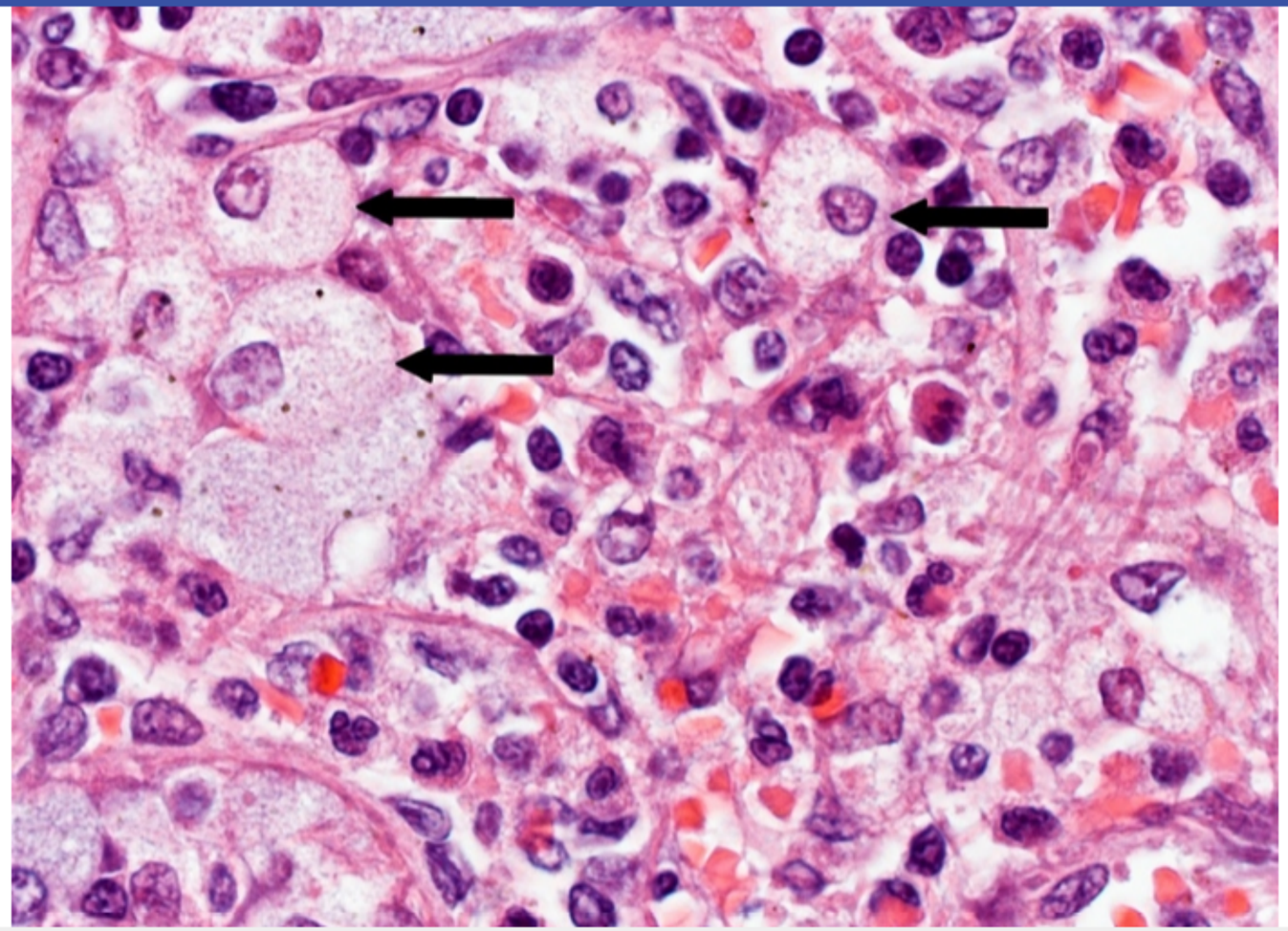
Educational objective:
In Niemann-Pick disease, sphingomyelinase deficiency causes accumulation of the lipid sphingomyelin. Clinical features include hepatosplenomegaly, neurologic regression, and a cherry-red macular spot in infancy.

References

- Types A and B Niemann-Pick disease.
- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly

Niemann-Pick disease is an autosomal recessive disorder common among Ashkenazi Jews and is characterized by **sphingomyelinase**

Exhibit Display



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- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly

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Niemann-Pick disease is an autosomal recessive disorder common among Ashkenazi Jews and is characterized by **sphingomyelinase**

Exhibit Display

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- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly

These lipid-laden foam cells (black arrows) accumulate in the liver and spleen and cause **hepatosplenomegaly**. Progressive neuronal accumulation is responsible for **hypotonia** and **neurologic degeneration** (eg, failure to progress developmentally, loss of milestones). Retinal accumulation leads to a cherry-red macular spot (blue arrow). This patient presents with the classic infantile type A variant that results in hepatosplenomegaly, progressive neurologic deterioration, and death by age 3 years.

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In Niemann-Pick disease, sphingomyelinase deficiency causes accumulation of the lipid sphingomyelin. Clinical features include hepatosplenomegaly, neurologic regression, and a cherry-red macular spot in infancy.

References

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- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly

Biochemistry	Endocrine, Diabetes & Metabolism	Niemann pick
Subject	System	Topic

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A 3-day-old boy is brought to the office due to poor feeding, vomiting, and progressive lethargy. The parents also report that his diapers have a "burnt sugar smell" differing from their previous children's diapers. The mother and infant were discharged from the hospital yesterday after a normal pregnancy and spontaneous vaginal delivery. The mother is exclusively breastfeeding. Her other 2 children are healthy and have no medical problems. Physical examination shows a lethargic infant with dry mucous membranes and generalized hypertonia. Which of the following should be restricted from this infant's diet?

A. Galactose
B. Leucine
C. Methionine
D. Phenylalanine
E. Tyrosine

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- A. Galactose (8%)
- ✓ B. Leucine (71%)
- C. Methionine (2%)
- D. Phenylalanine (14%)
- E. Tyrosine (2%)

Omitted
Correct answer
B

71%
Answered correctly

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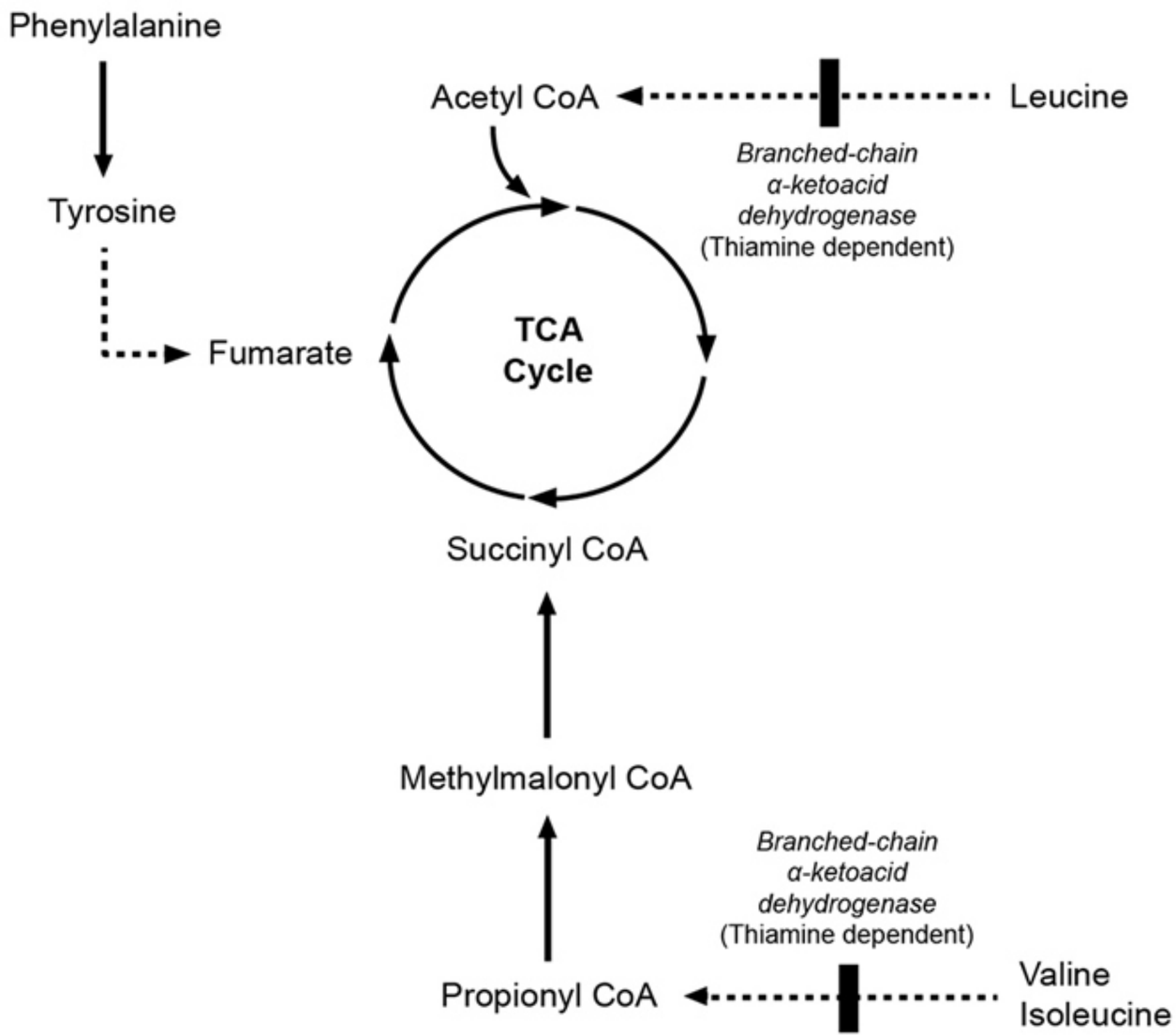
05/03/2020
Last Updated

Explanation


Phenylalanine
Tyrosine
Fumarate
Acetyl CoA
Leucine
Branched-chain α-ketoacid dehydrogenase (Thiamine dependent)
TCA Cycle
Succinyl CoA
Methylmalonyl CoA
Branched-chain α-ketoacid dehydrogenase (Thiamine dependent)
Propionyl CoA
Valine
Isoleucine

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This infant has symptoms typical of **maple syrup urine disease** (MSUD), an autosomal recessive inborn error of metabolism due to branched-chain α-ketoacid dehydrogenase complex (BCKDC) deficiency. This enzyme normally allows for the breakdown of **leucine**, **isoleucine**, and **valine** into substrates for entry into the TCA cycle.

BCKDC deficiency is **neurotoxic** primarily due to elevated levels of leucine. Infants present in the first few days of life with progressive irritability, poor feeding, lethargy, and increased muscle tone. The urine characteristically has a sweet, **"maple syrup" odor**. Diagnosis can be confirmed by the presence of **elevated branched-chain amino acid levels**. Therapy consists of **dietary restriction** of branched-chain amino acids, but patients remain at lifelong risk for neurotoxicity in the setting of intercurrent illnesses and fasting.

(Choice A) Galactosemia is an autosomal recessive disorder due to galactose-1-phosphate uridyltransferase deficiency. The buildup of galactose (normally found in breast milk and regular infant formula) leads to neonatal jaundice, cataracts, hepatomegaly, and frequently *Escherichia coli* sepsis. Dietary restriction of galactose is the mainstay of treatment.

(Choice C) Homocystinuria is an autosomal recessive disorder marked by a defect in cystathionine β-synthase, resulting in elevated levels of homocysteine and methionine. Restriction of methionine for these patients is one aspect of therapy.

(Choice D) Phenylketonuria is an autosomal recessive disorder characterized by phenylalanine hydroxylase deficiency, leading to hyperphenylalaninemia. Untreated patients develop intellectual disability, seizures, decreased hair/skin pigmentation, and a "musty" odor.

(Choice E) Dietary tyrosine restriction may be beneficial for patients with hypertyrosinemia (progressive liver and renal disease) or alkaptonuria (pigmented osteoarthritis).

Educational objective:
Maple syrup urine disease classically presents with irritability, dystonia, poor feeding, and a "maple syrup" scent to the patient's urine within the first few days of life. Dietary restriction of branched-chain amino acids (eg, leucine, isoleucine, valine) is the hallmark of treatment.

References

- Branched-chain amino acid metabolism: From rare Mendelian diseases to more common disorders.
- Maple syrup urine disease

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A 15-year-old boy is being evaluated for poor exercise endurance. He recently started weightlifting with some of his friends and is disappointed that he is "the weakest one by far." He says he tries as hard as possible, but his "arms feel like jelly after just a few repetitions." The patient also says he sometimes experiences severe muscle cramping and urine discoloration after periods of intense straining. Further evaluation reveals that his exercise tolerance can be greatly improved by drinking an oral glucose solution before beginning a strenuous activity. This patient is most likely deficient in an enzyme that catalyzes which of the following conversions?

A. A
B. B
C. C
D. D
E. E

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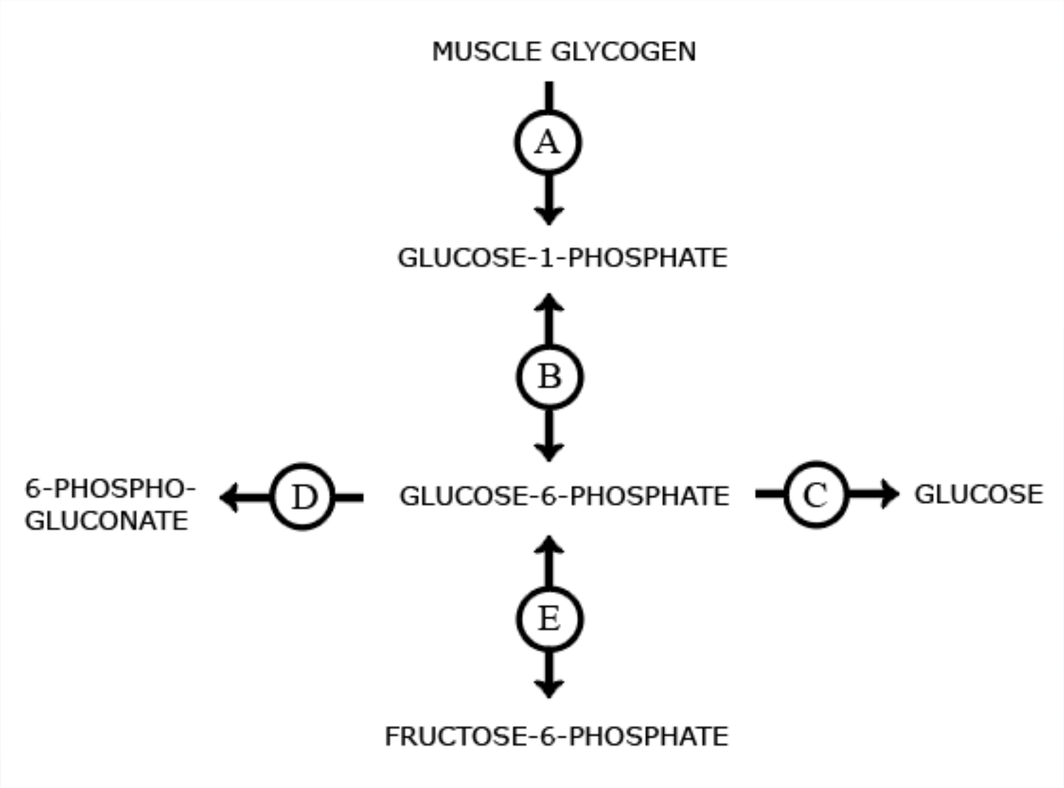

A. A

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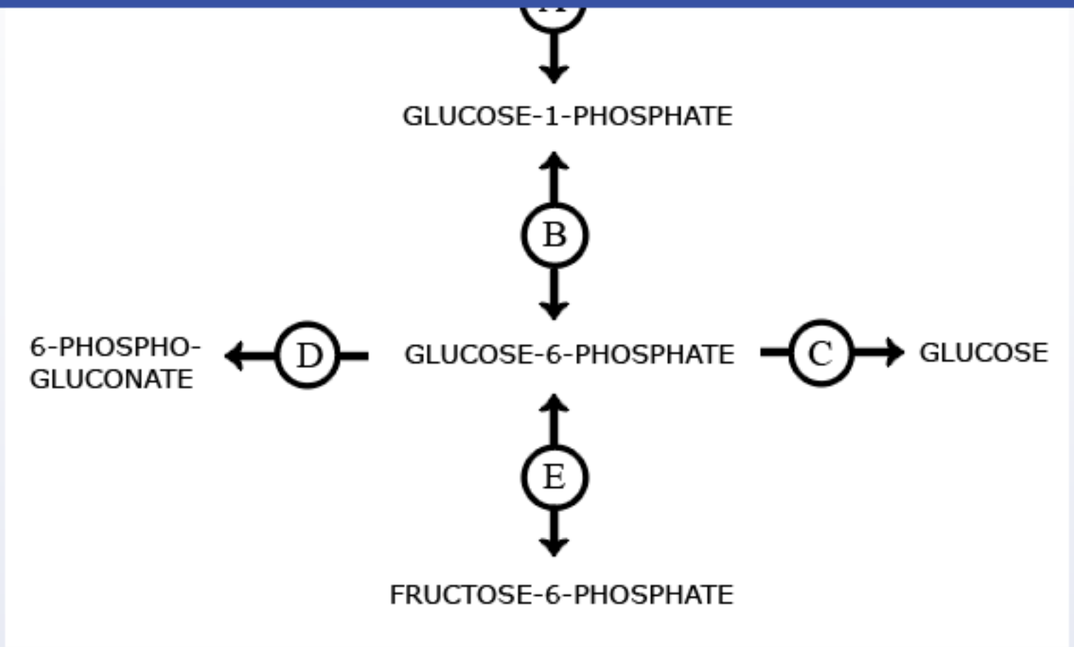

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D. D
E. E

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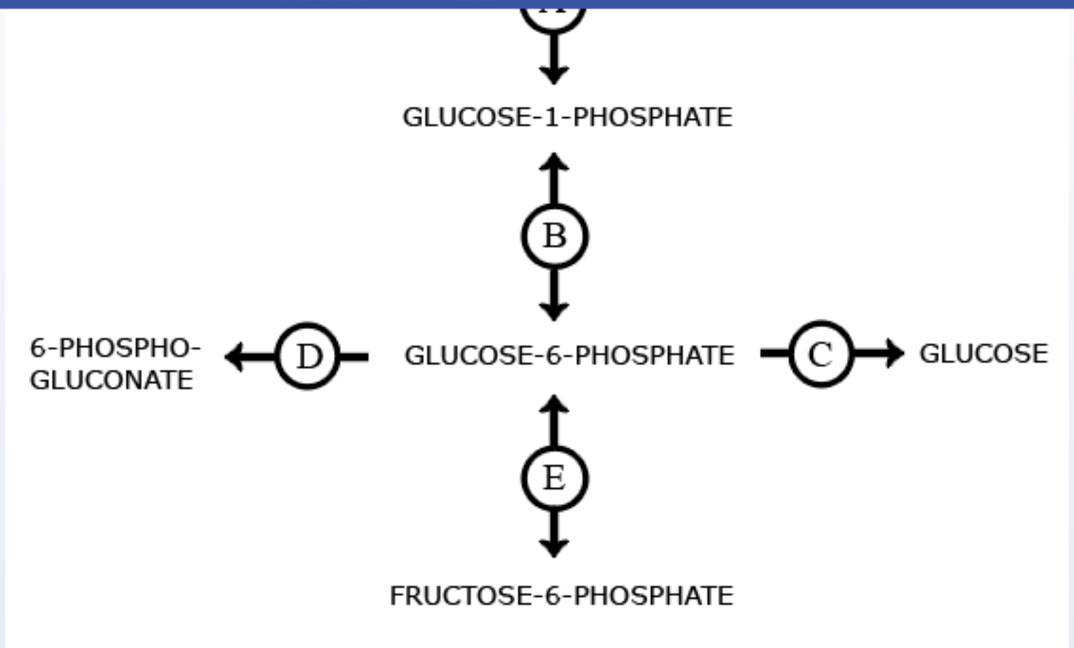

- ✓ A. A (67%)
- B. B (9%)
- C. C (18%)
- D. D (1%)
- E. E (1%)

Omitted
Correct answer

67%
Answered correctly

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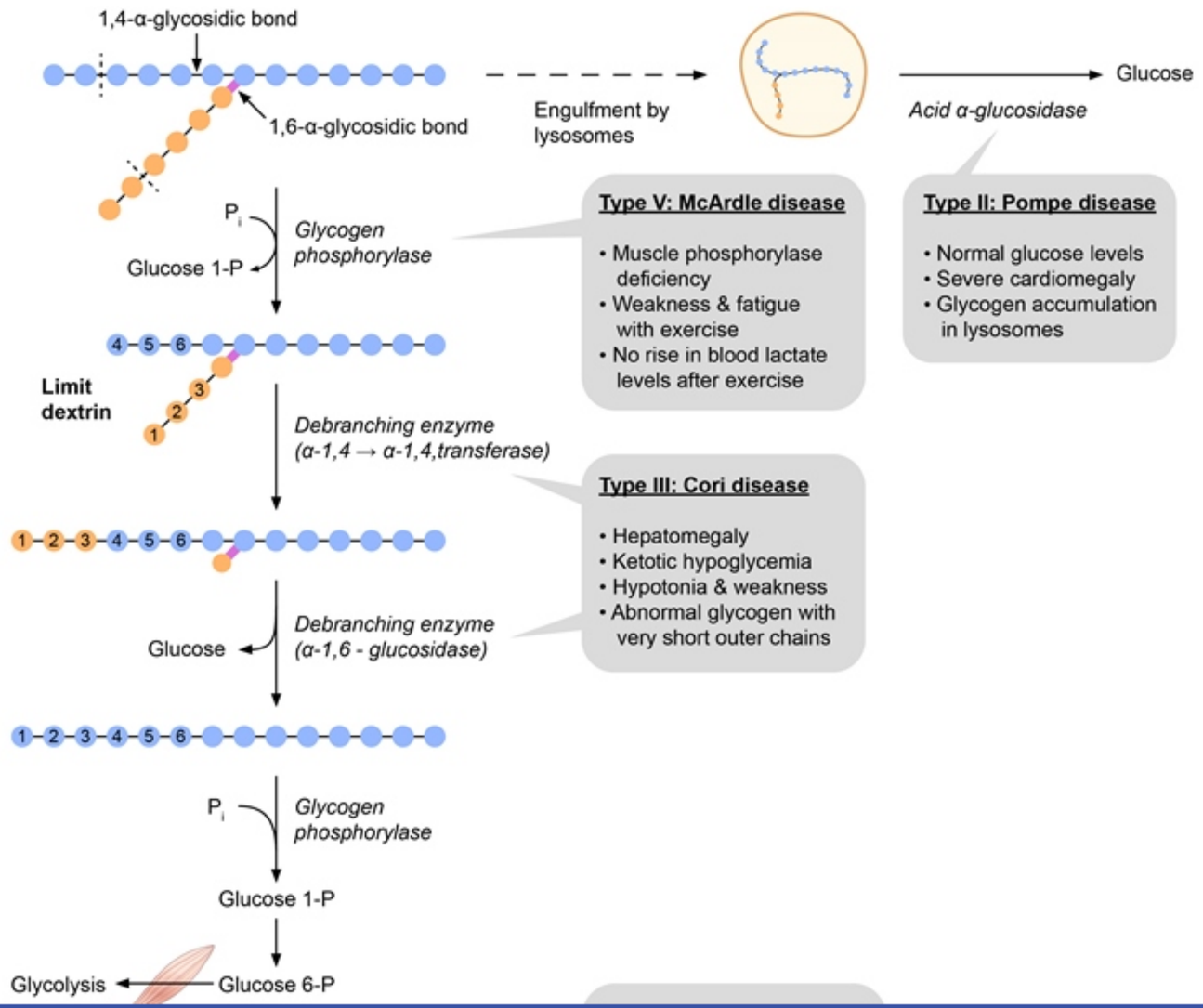
Impairments in glycogenolysis



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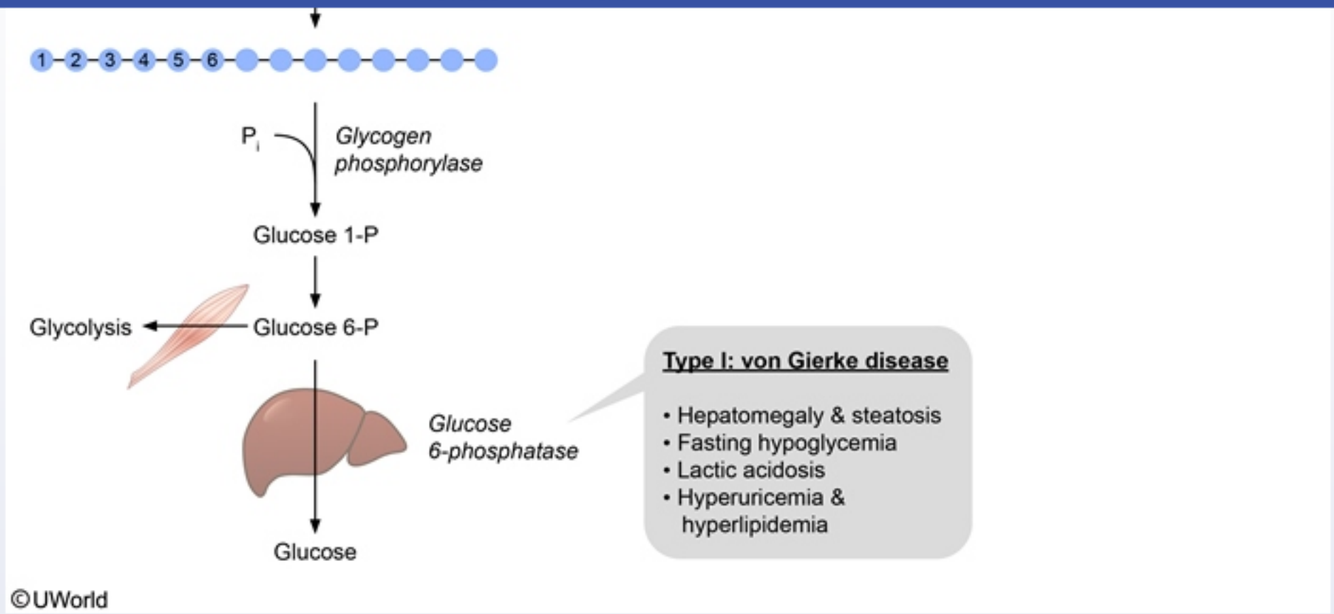

This patient most likely has **McArdle disease** (glycogen storage disease type V). This condition is caused by deficiency of **myophosphorylase**, an isoenzyme of glycogen phosphorylase present in muscle tissue. Deficiency of this enzyme leads to decreased breakdown of glycogen during exercise, resulting in **poor exercise tolerance**, **muscle cramps**, and **rhabdomyolysis**. The prognosis is generally good and symptoms can be improved by consuming simple sugars before beginning physical activity.

During glycogenolysis, **glycogen phosphorylase** shortens glycogen chains by cleaving α-1,4-glycosidic linkages between glucose residues, liberating glucose 1-phosphate in the process. This occurs until 4 residues remain before a branch point (the "limit" dextrin). At this point, the debranching enzyme performs 2 enzymatic functions:

1. Glucosyltransferase cleaves the 3 outer glucose residues of the 4 that are left by glycogen phosphorylase and transfers them to a nearby branch
2. The enzyme α-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

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(Choice B) The glucose 1-phosphate generated by glycogenolysis is converted by phosphoglucomutase to glucose 6-phosphate, which can then undergo glycolysis.

(Choice C) Within the liver and kidney, glucose 6-phosphatase converts glucose 6-phosphate to glucose to help maintain blood glucose levels during periods of fasting. However, muscles lack glucose 6-phosphatase and so must utilize glucose 6-phosphate for glycolysis during muscle contraction.

(Choice D) The first step in the pentose phosphate pathway (hexose monophosphate pathway) is conversion of glucose 6-phosphate to 6-phosphogluconate by glucose-6-phosphate dehydrogenase. This pathway maintains cellular NADPH levels and produces pentose sugars for nucleotide synthesis.

(Choice E) Glucose 6-phosphate is converted into fructose 6-phosphate by glucose 6-phosphate isomerase during the second step of glycolysis.

Educational objective:
Glycogen serves as a source of glucose during fasting and as an energy store that can be mobilized quickly during strenuous muscle contraction. Myophosphorylase deficiency (McArdle disease or glycogen storage disease type V) causes failure of muscle glycogenolysis, resulting in

debranching enzyme performs 2 enzymatic functions:

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(Choice B) The glucose 1-phosphate generated by glycogenolysis is converted by phosphoglucomutase to glucose 6-phosphate, which can then undergo glycolysis.

(Choice C) Within the liver and kidney, glucose 6-phosphatase converts glucose 6-phosphate to glucose to help maintain blood glucose levels during periods of fasting. However, muscles lack glucose 6-phosphatase and so must utilize glucose 6-phosphate for glycolysis during muscle contraction.

(Choice D) The first step in the pentose phosphate pathway (hexose monophosphate pathway) is conversion of glucose 6-phosphate to 6-phosphogluconate by glucose-6-phosphate dehydrogenase. This pathway maintains cellular NADPH levels and produces pentose sugars for nucleotide synthesis.

(Choice E) Glucose 6-phosphate is converted into fructose 6-phosphate by glucose 6-phosphate isomerase during the second step of glycolysis.

Educational objective:
Glycogen serves as a source of glucose during fasting and as an energy store that can be mobilized quickly during strenuous muscle contraction. Myophosphorylase deficiency (McArdle disease or glycogen storage disease type V) causes failure of muscle glycogenolysis, resulting in decreased exercise tolerance, muscle pain and cramping, and myoglobinuria with physical activity.

Biochemistry	Endocrine, Diabetes & Metabolism	Glycogen storage disease
Subject	System	Topic

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An 8-month-old boy is evaluated for developmental delay, failure to thrive, and episodic seizures. Physical examination shows ophthalmoplegia and hypotonia. Laboratory studies reveal an elevated serum lactate level. Further histochemical studies show severely reduced pyruvate dehydrogenase enzyme activity in both freshly isolated peripheral blood lymphocytes and cultured fibroblasts. Increasing which of the following substances in his diet is most likely to help this patient generate energy without further elevating lactate levels?

- A. Alanine
- B. Asparagine
- C. Galactose
- D. Glycerol
- E. Lysine
- F. Serine

Submit

An 8-month-old boy is evaluated for developmental delay, failure to thrive, and episodic seizures. Physical examination shows ophthalmoplegia and hypotonia. Laboratory studies reveal an elevated serum lactate level. Further histochemical studies show severely reduced pyruvate dehydrogenase enzyme activity in both freshly isolated peripheral blood lymphocytes and cultured fibroblasts. Increasing which of the following substances in his diet is most likely to help this patient generate energy without further elevating lactate levels?

- A. Alanine (32%)
- B. Asparagine (10%)
- C. Galactose (7%)
- D. Glycerol (14%)
- ✓ E. Lysine (32%)
- F. Serine (2%)

Omitted
Correct answer
E

32%
Answered correctly

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04/20/2020
Last Updated

Explanation

This patient has **pyruvate dehydrogenase deficiency**, an inherited inborn error of metabolism often presenting in infancy with lactic acidosis and neurologic defects. The disease results from deficient activity of the pyruvate dehydrogenase complex, a multi-enzyme complex generating acetyl-CoA from pyruvate, thereby linking glycolysis and the TCA cycle. Dietary carbohydrates are broken down into pyruvate via glycolysis; in patients with pyruvate dehydrogenase deficiency, the lack of enzymatic activity leads to a **buildup of pyruvate**, which is shunted to lactate via

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Disease management involves the implementation of a **ketogenic diet**: a high-fat, low-carbohydrate diet with moderate levels of protein. This diet forces the production of ketone bodies from fat and amino acid catabolism to fuel the body in the place of glucose. The near-absence of glucose in the diet decreases the amount of pyruvate generated, thereby decreasing lactate levels.

Amino acid catabolism results in formation of intermediates that are referred to as glucogenic, ketogenic, or both. Glucogenic amino acid metabolism produces pyruvate or TCA cycle intermediates, which can be converted to glucose via gluconeogenesis. Ketogenic amino acid metabolism generates the ketone body precursor acetyl-CoA. **Lysine** and **leucine** are **exclusively ketogenic** amino acids; they cannot be metabolized to pyruvate and consumption will not lead to increased production of lactic acid.

(Choices A and F) The non-essential glucogenic amino acids alanine and serine can be converted to pyruvate through a transamination reaction catalyzed by alanine transaminase and a deamination reaction catalyzed by serine dehydratase, respectively.

(Choice B) Asparagine is catabolized to aspartate and subsequently transaminated to produce glutamate and oxaloacetate, an intermediate of the TCA cycle. Oxaloacetate by itself cannot be used to produce energy; it must first undergo condensation with acetyl-CoA to form citrate.

(Choice C) The monosaccharide galactose is metabolized in the glycolytic pathway; dietary intake will result in elevated levels of lactate in patients with pyruvate dehydrogenase deficiency.

(Choice D) Glycerol is metabolized to glyceraldehyde 3-phosphate, a glycolysis intermediate. It can be used as a substrate to form pyruvate and, subsequently, lactate.

Educational objective:
Pyruvate dehydrogenase complex deficiency is an inherited inborn error of metabolism causing lactic acidosis and neurologic defects. Patients are unable to convert pyruvate to acetyl-CoA, resulting in a shunting of pyruvate to lactic acid. In these patients, metabolism of exclusively ketogenic amino acids (eg, lysine, leucine) can provide energy in the form of acetyl-CoA without increasing lactate production.

in the diet decreases the amount of pyruvate generated, thereby decreasing lactate levels.

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Educational objective:
Pyruvate dehydrogenase complex deficiency is an inherited inborn error of metabolism causing lactic acidosis and neurologic defects. Patients are unable to convert pyruvate to acetyl-CoA, resulting in a shunting of pyruvate to lactic acid. In these patients, metabolism of exclusively ketogenic amino acids (eg, lysine, leucine) can provide energy in the form of acetyl-CoA without increasing lactate production.

References

- Outcome of pyruvate dehydrogenase deficiency treated with ketogenic diets. Studies in patients with identical mutations.

Biochemistry	Endocrine, Diabetes & Metabolism	Tca cycle
Subject	System	Topic

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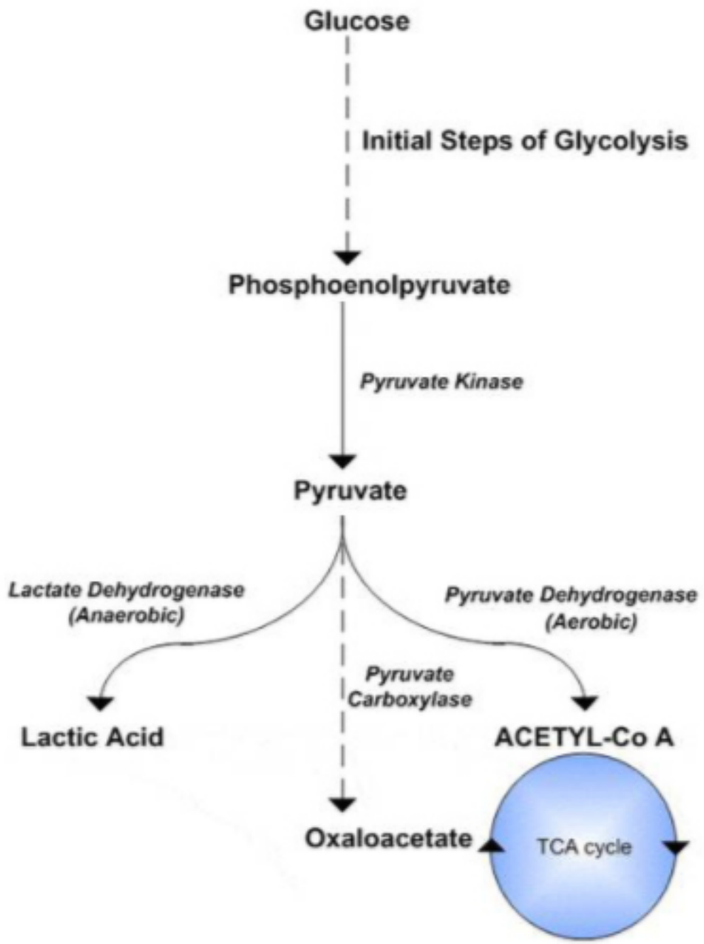
D. Glycerol (14%)

Exhibit Display



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(Choices A and F) The non-essential glucogenic amino acids alanine and serine can be converted to pyruvate through a transamination reaction

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A 6-year-old girl is brought to the office for evaluation of short stature. Her parents have noticed that she bears little resemblance to her 2 older siblings. The patient's mother and father are 172.5 cm (5'8") and 183 cm (6') tall, respectively. On physical examination, the patient's height is 3 standard deviations below the mean for her age. Other findings include low-set ears, a high arched palate, a webbed neck, and cubitus valgus. Chromosomal analysis reveals a 45,XO karyotype. The patient is started on a medication to improve growth and normalize her height. Which of the following intracellular pathways is stimulated by the medication used in this patient?

A. Binding of activated receptors to DNA to modify transcription

B. Cyclic AMP-Protein kinase A pathway

C. Diacylglycerol-Protein kinase C pathway

D. Inositol triphosphate–calcium–calmodulin pathway

E. JAK-STAT pathway

Submit

A 6-year-old girl is brought to the office for evaluation of short stature. Her parents have noticed that she bears little resemblance to her 2 older siblings. The patient's mother and father are 172.5 cm (5'8") and 183 cm (6') tall, respectively. On physical examination, the patient's height is 3 standard deviations below the mean for her age. Other findings include low-set ears, a high arched palate, a webbed neck, and cubitus valgus. Chromosomal analysis reveals a 45,XO karyotype. The patient is started on a medication to improve growth and normalize her height. Which of the following intracellular pathways is stimulated by the medication used in this patient?

- A. Binding of activated receptors to DNA to modify transcription (22%)
- B. Cyclic AMP-Protein kinase A pathway (13%)
- C. Diacylglycerol-Protein kinase C pathway (3%)
- D. Inositol triphosphate–calcium–calmodulin pathway (5%)
- ✓ E. JAK-STAT pathway (54%)

Omitted
Correct answer
E

54%
Answered correctly

02 secs
Time Spent

04/26/2020
Last Updated

Explanation

Hepatic growth hormone receptors

Growth

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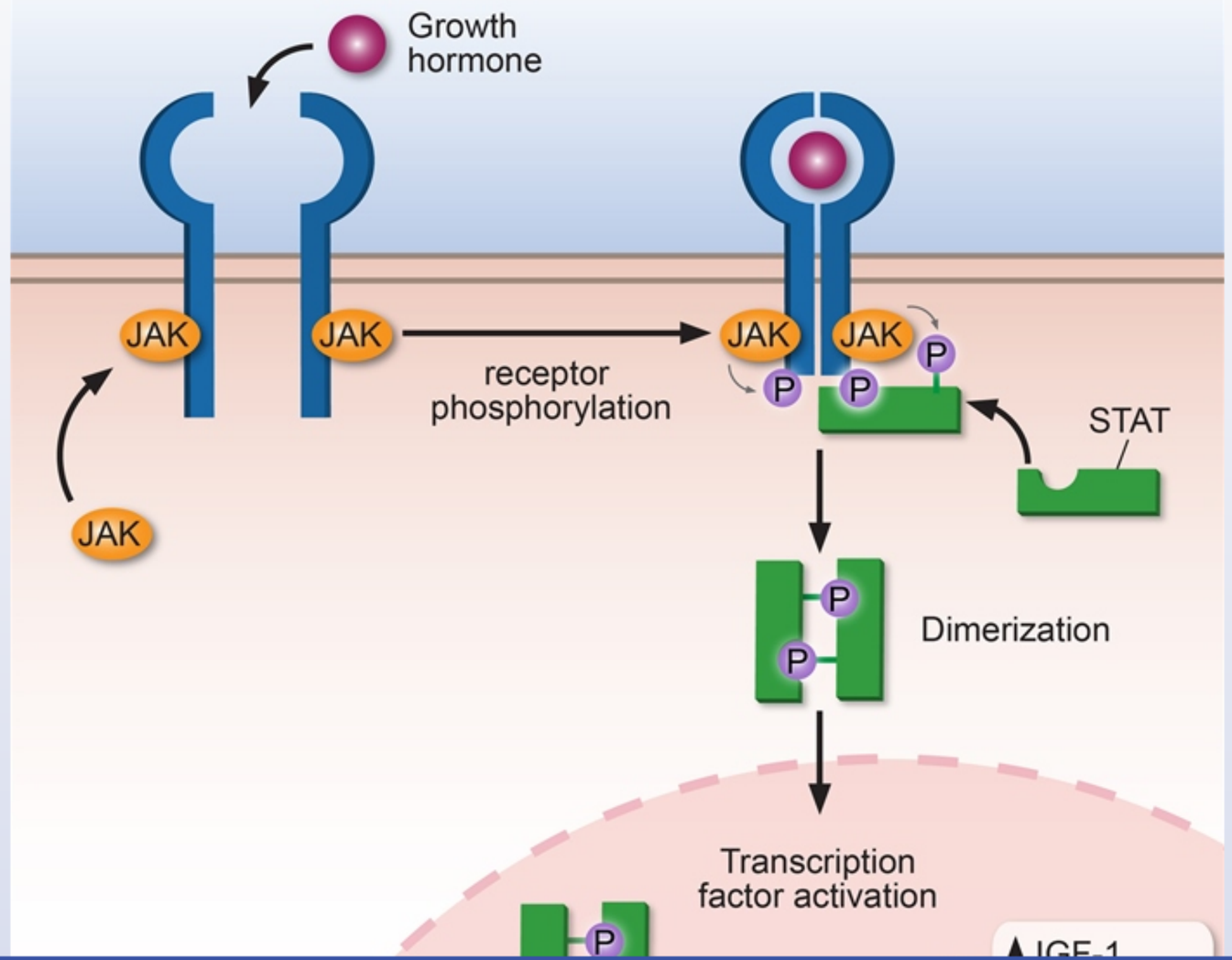
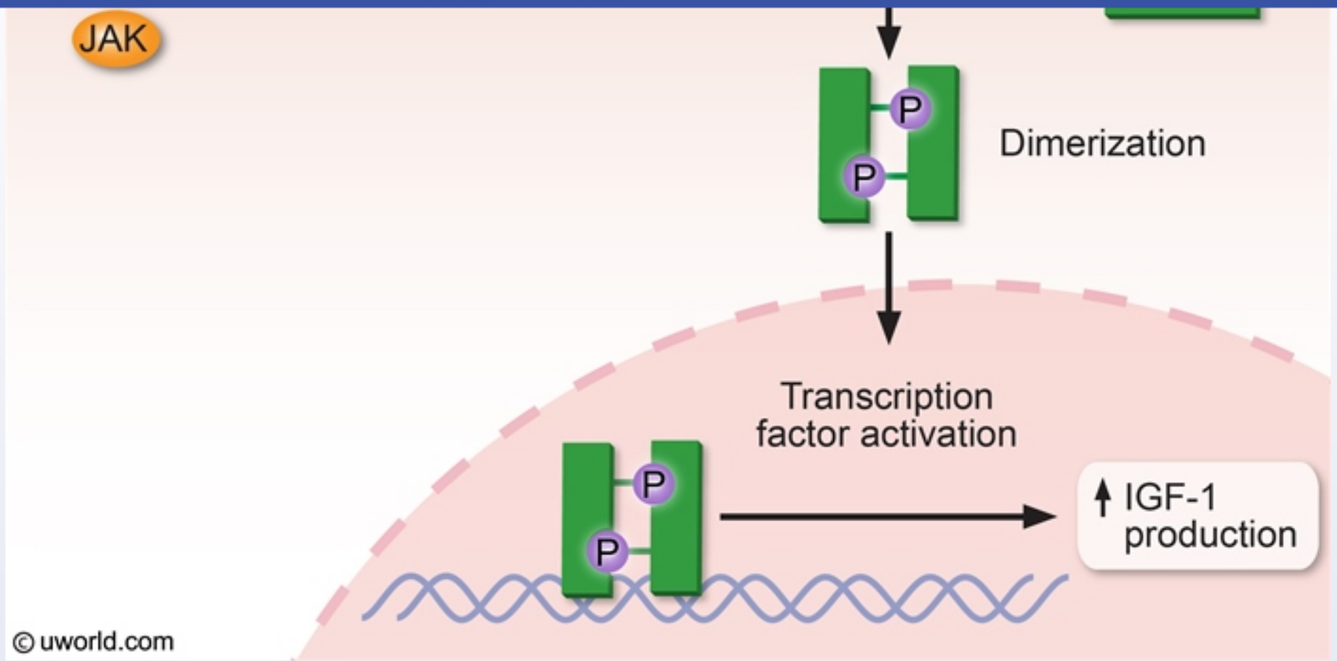
Hepatic growth hormone receptors





This patient with a 45,XO karyotype has Turner syndrome. Individuals with this condition are typically treated with **growth hormone** (GH) when growth failure becomes evident, leading to normalization of height in most patients.

GH promotes growth by acting on the cell surface receptors that stimulate production of insulin-like growth factor-1 (IGF-1), primarily in the liver. One GH molecule binds to 2 receptors on the cell surface, leading to activation of **Janus kinase (JAK)**, a **nonreceptor tyrosine kinase**. JAK subsequently phosphorylates several tyrosine residues in the intracellular domain of the GH receptor. These phosphorylated tyrosine residues function as docking sites for **STAT** (**signal transducer and activator of transcription**). Once STAT is recruited to the receptor, it is also phosphorylated by JAK. STAT then dimerizes and translocates to the nucleus, where it induces *IGF-1* gene transcription by binding to the promoter region. Other molecules that use the JAK-STAT pathway include cytokines (eg, interferon) and hematopoietic growth factors (eg, erythropoietin, G-CSF).

(Choice A) Steroid and thyroid hormones bind to intracellular receptors. Once these receptors are activated, they subsequently bind to the promoter region of target genes to modify transcription.

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(Choice A) Steroid and thyroid hormones bind to intracellular receptors. Once these receptors are activated, they subsequently bind to the promoter region of target genes to modify transcription.

(Choice B) Several hormones (eg, PTH, ACTH, TSH, ADH [V2 receptor]) activate adenylyl cyclase after binding to G protein-coupled receptors on the cell membrane. Adenylyl cyclase converts ATP to cyclic AMP, which subsequently activates protein kinase A.

(Choices C and D) Various hormones (eg, GnRH, TRH, angiotensin II, ADH [V1 receptor]) function by binding to G protein-coupled receptors that activate phospholipase C. Activated phospholipase C hydrolyzes phosphatidylinositol bisphosphate to inositol triphosphate (IP_3) and diacylglycerol (DAG). IP_3 mobilizes calcium from the endoplasmic reticulum, and DAG directly activates protein kinase C.

Educational objective:
Growth hormone binds to cell surface receptors, leading to intracellular activation of the JAK-STAT pathway. Cytokines (eg, interferon) and hematopoietic growth factors (eg, erythropoietin, G-CSF) also use this pathway.

References

- The role of STAT proteins in growth hormone signaling.

Biochemistry Endocrine, Diabetes & Metabolism Turner syndrome

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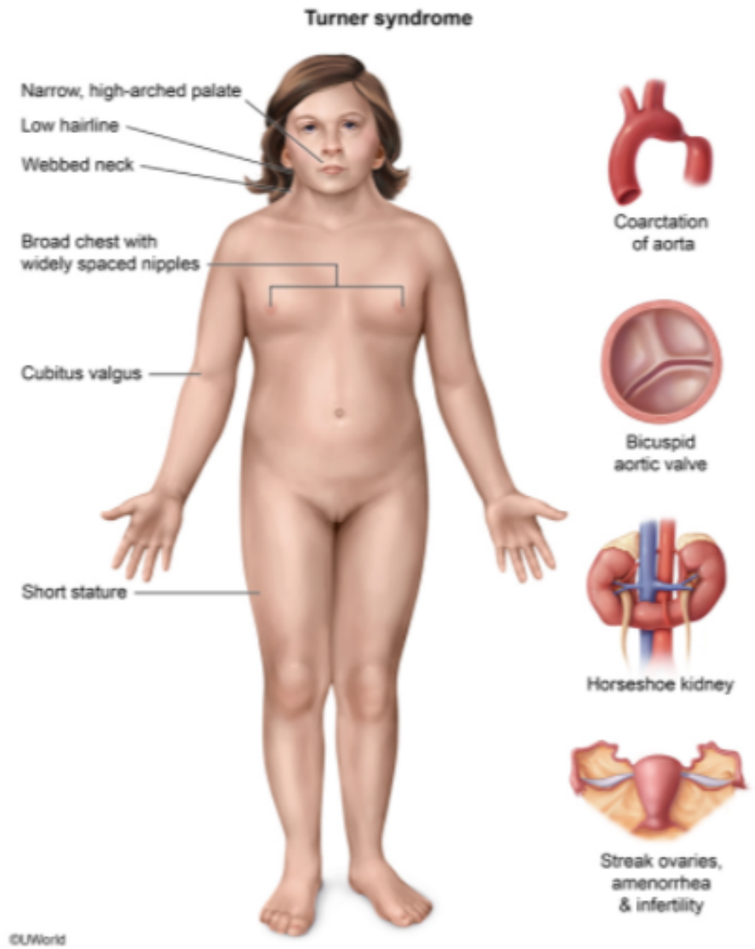

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Biochemistry | Endocrine, Diabetes & Metabolism | Turner syndrome

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References

- The role of STAT proteins in growth hormone signaling.

Biochemistry	Endocrine, Diabetes & Metabolism	Turner syndrome
Subject	System	Topic

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A research scientist studying the metabolic pathways that contribute to obesity feeds experimental animals a high-carbohydrate, high-protein diet for a prolonged period. A sample of liver tissue is then obtained from the animals, and the activity of various enzymes involved in fatty acid metabolism is measured and recorded. It is determined that beta-oxidation of fatty acids is inhibited within these cells as a result of the diet. An increase in which of the following substances is most likely responsible for the observed effect?

A. Acetoacetate

B. Carnitine

C. Citrate

D. Malonyl-CoA

E. NADPH

Submit

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- A. Acetoacetate (10%)
- B. Carnitine (18%)
- C. Citrate (18%)
- ✓ D. Malonyl-CoA (38%)
- E. NADPH (13%)

Omitted
Correct answer
D

38%
Answered correctly

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Time Spent

04/25/2020
Last Updated

Explanation

In the **well-fed state**, the abundance of ATP in hepatocytes inhibits isocitrate dehydrogenase, leading to high levels of citrate in the mitochondria. Citrate is transferred to the cytosol via the citrate shuttle and cleaved by ATP citrate lyase to form acetyl-CoA. High citrate levels (in addition to elevated insulin caused by high carbohydrate intake) causes upregulation of **Acetyl-CoA carboxylase**. This cytosolic enzyme catalyzes the conversion of acetyl-CoA to malonyl-CoA in the rate-limiting step of de novo **fatty acid synthesis**. Fatty acid synthase then catalyzes the condensation of malonyl-CoA with acetyl-CoA to create a 4-carbon molecule that will undergo subsequent condensation reactions to form a 16-carbon fatty acid.

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Beta-oxidation of fatty acids takes place primarily within the **mitochondrial matrix**. Mitochondrial membranes are impermeable to fatty acids due to their negative charge, so a specialized membrane carrier (**carnitine**) must be used to shuttle them into the matrix. **Malonyl-CoA inhibits carnitine acyltransferase**, preventing the transfer of acyl groups into the mitochondria. This inhibitory action functions to prevent the breakdown of newly synthesized fatty acids.

(Choice A) Ketone bodies (eg, acetoacetate) are a major source of fuel for muscle, brain, and cardiac tissue that are produced during times of starvation or fasting when oxaloacetate is in short supply and acetyl-CoA is in excess.

(Choice B) Carnitine is an amino acid that is essential for the transport of fatty acids through the mitochondrial membrane. It is a necessary component of fatty acid oxidation.

(Choice C) Citrate is an intermediate in the TCA cycle. It can be exported out of the mitochondrial matrix and into the cytosol, where it is broken down into acetyl-CoA for use in de novo fatty acid synthesis.

(Choice E) NADPH is a reducing molecule necessary for the synthesis of fatty acids. In contrast, beta-oxidation of fats produces $FADH_2$ and NADH-reducing equivalents.

Educational objective:
Cytosolic acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA during the rate-limiting step of de novo fatty acid synthesis. Malonyl-CoA also inhibits the action of mitochondrial carnitine acyltransferase, thereby inhibiting beta-oxidation of newly formed fatty acids.

References

- Malonyl-CoA: the regulator of fatty acid synthesis and oxidation.

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References

- Malonyl-CoA: the regulator of fatty acid synthesis and oxidation.

Biochemistry	Endocrine, Diabetes & Metabolism	Beta oxidation
Subject	System	Topic

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A 35-year-old man comes to the office with progressively worsening fatigue associated with dark urine and back pain. Two days ago, the patient ate some large, flat beans brought home by his wife after a business trip to Egypt. Physical examination shows jaundice and pallor. Laboratory results reveal a hemoglobin level of 8 g/dL. Further evaluation reveals deficiency of an enzyme involved in the conversion of glucose-6-phosphate to ribulose-5-phosphate. The substance generated during this conversion is necessary for which of the following biochemical processes?

- A. ADP phosphorylation
- B. Fatty acid synthesis
- C. Glycogen storage
- D. Ketone body synthesis
- E. Protein degradation

Submit

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- A. ADP phosphorylation (29%)
- ✓ B. Fatty acid synthesis (44%)
- C. Glycogen storage (9%)
- D. Ketone body synthesis (8%)
- E. Protein degradation (8%)

Omitted
Correct answer
B

44%
Answered correctly

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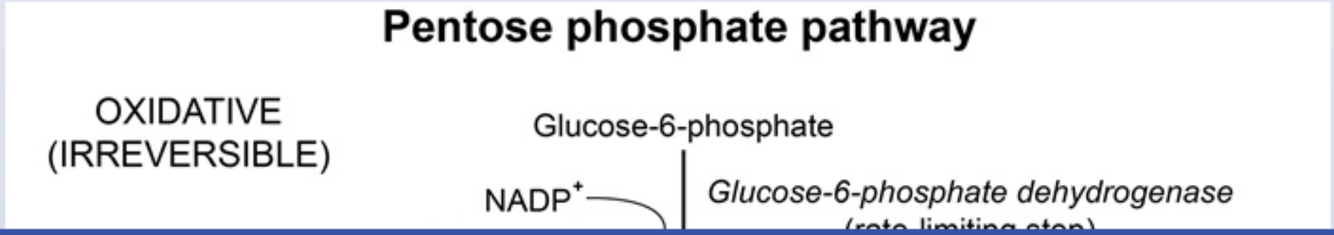
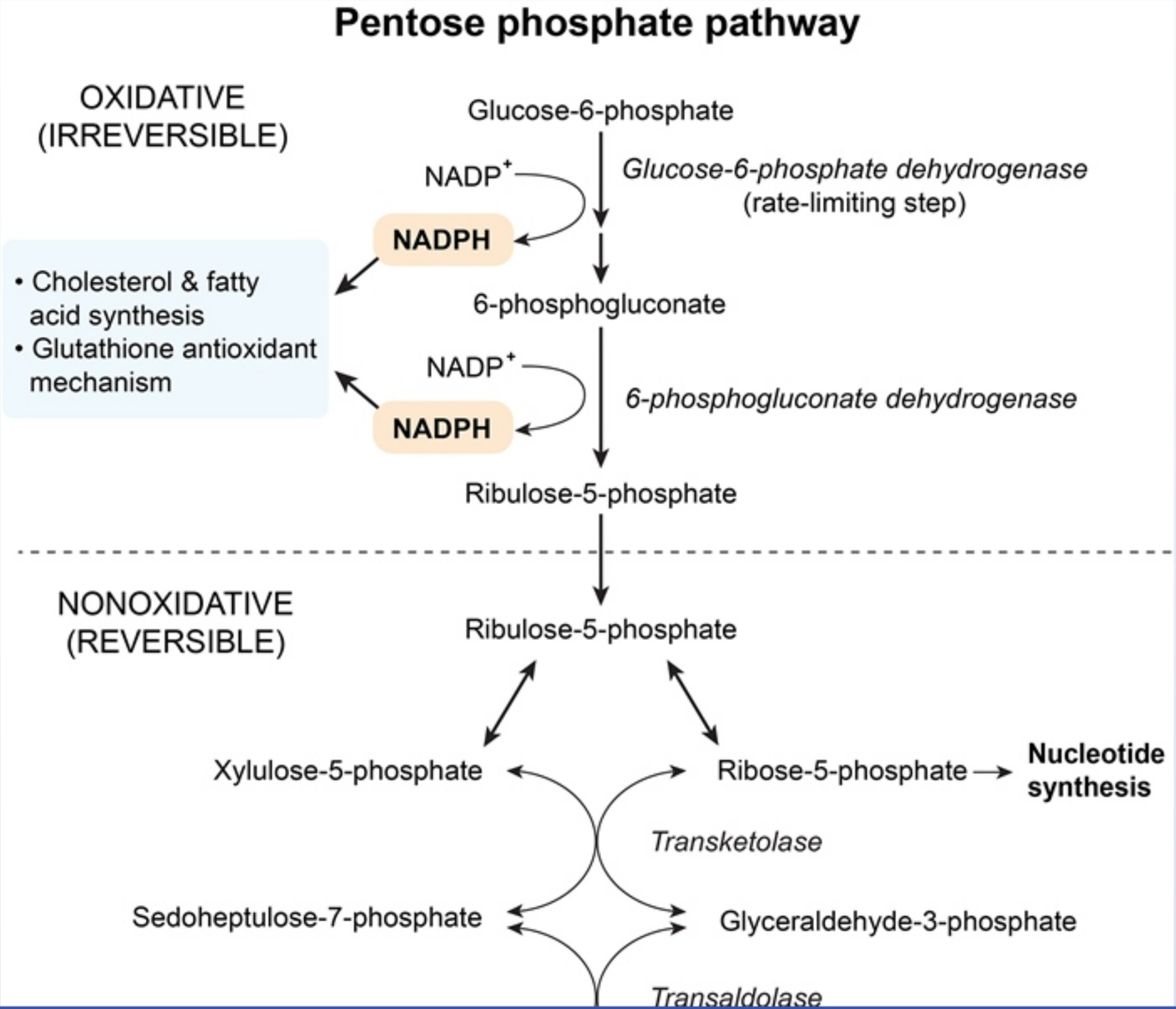
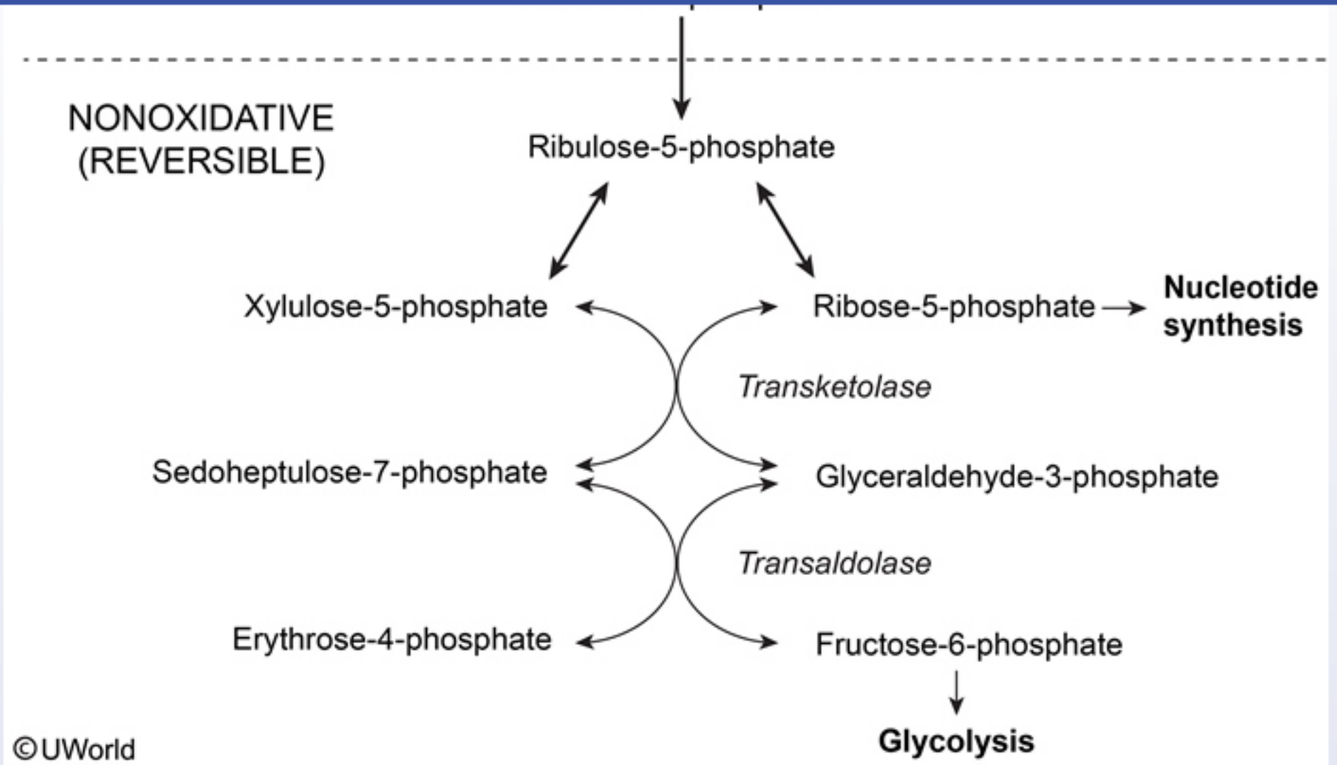
Time Spent

05/11/2020
Last Updated

Explanation




Pentose phosphate pathway
OXIDATIVE
(IRREVERSIBLE)
Glucose-6-phosphate
NADP+
Glucose-6-phosphate dehydrogenase
(rate-limiting step)
NADPH
• Cholesterol & fatty acid synthesis
• Glutathione antioxidant mechanism
6-phosphogluconate
NADP+
6-phosphogluconate dehydrogenase
NADPH
Ribulose-5-phosphate
NONOXIDATIVE
(REVERSIBLE)
Ribulose-5-phosphate
Xylulose-5-phosphate
Ribose-5-phosphate
Nucleotide synthesis
Transketolase
Sedoheptulose-7-phosphate
Glyceraldehyde-3-phosphate
Transaldolase



This patient most likely has **glucose-6-phosphate dehydrogenase (G6PD) deficiency**. G6PD catalyzes the first step in the pentose phosphate pathway (PPP), the oxidative portion of which generates 2 molecules of NADPH while converting glucose-6-phosphate to ribulose-5-phosphate. The nonoxidative reactions of the PPP reversibly convert ribulose-5-phosphate into ribose-5-phosphate (substrate for nucleotide synthesis) or glycolytic intermediates that can be used for energy production.

Because the PPP is the **main source of NADPH**, the pathway is particularly active in:

- Cells experiencing **high oxidative stress** (eg, erythrocytes) in which NADPH is used to regenerate reduced glutathione, an antioxidant that helps maintain cell integrity
- Organs such as the liver and adrenal cortex that are involved in **reductive biosynthesis** (eg, synthesis of fatty acids, cholesterol, steroids)

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- Organs such as the liver and adrenal cortex that are involved in **reductive biosynthesis** (eg, synthesis of fatty acids, cholesterol, steroids) and cytochrome P450 metabolism
- Phagocytic cells generating a respiratory burst via NADPH oxidase

In patients with G6PD deficiency, erythrocytes are unable to maintain a sufficient supply of reduced glutathione during periods of increased oxidative stress, which can occur with certain infections (eg, pneumonia, viral hepatitis), consumption of fava beans, or specific medications (eg, primaquine, sulfa drugs). The resulting oxidative damage causes **acute hemolytic anemia** and jaundice.

(Choice A) NADH can be used as a reducing agent to convert ADP to ATP during oxidative phosphorylation. In contrast to NADH, NADPH cannot be used to convert ADP into ATP.

(Choice C) Glycogenesis is the process by which glucose is stored for later use through the addition of glucose molecules to glycogen chains. It does not require NADPH.

(Choice D) Ketone bodies are formed mainly in the liver during times of fasting when there is increased fat degradation. Cytosolic HMG-CoA synthase is the starting point of cholesterol synthesis whereas the mitochondrial version of the enzyme is the rate-limiting step in ketone body synthesis. Unlike cholesterol synthesis, ketone body production does not require NADPH.

(Choice E) Protein catabolism begins with the hydrolysis of polypeptides into amino acids. These subsequently undergo transamination reactions that funnel the amine nitrogen predominately into glutamate, which is oxidatively deaminated to produce ammonia. The urea cycle then converts ammonia into urea for elimination in the urine.

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Educational objective:
Glucose-6-phosphate dehydrogenase is the rate-limiting enzyme in the pentose phosphate pathway, the major source of cellular NADPH. This molecule is necessary for reducing glutathione (protects red blood cells from oxidative damage) and for the biosynthesis of cholesterol, fatty acids, and steroids.

Biochemistry	Endocrine, Diabetes & Metabolism	Hyperphosphatemia
Subject	System	Topic

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A healthy 34-year-old coal mine worker is trapped underground following partial collapse of an access shaft. Rescue efforts are directed toward clearing the obstructed tunnel, but it takes 2 days to reach him. While being taken to the surface, the miner tells rescuers that he feels dizzy and weak. He had an emergency supply of water but has not eaten anything for over 30 hours. Fingerstick blood glucose concentration is 78 mg/dL. Which of the following biochemical reactions is most likely responsible for maintaining this patient's current blood glucose levels?

A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA

B. Acetyl CoA → palmitic acid

C. Fructose 6-phosphate → fructose 1,6-bisphosphate

D. Glycogen → glucose-1-phosphate

E. Oxaloacetate → phosphoenolpyruvate

Submit

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- A. Acetoacetyl CoA → 3-hydroxy-3-methylglutaryl-CoA (13%)
- B. Acetyl CoA → palmitic acid (7%)
- C. Fructose 6-phosphate → fructose 1,6-bisphosphate (3%)
- D. Glycogen → glucose-1-phosphate (25%)
- ✓ E. Oxaloacetate → phosphoenolpyruvate (50%)

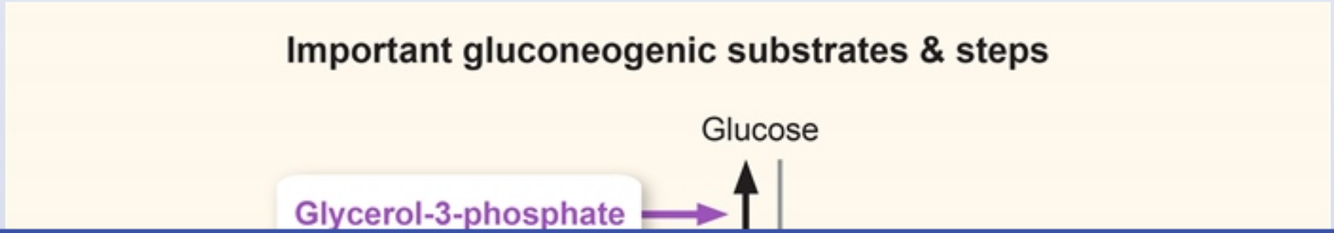
Omitted
Correct answer
E

50%
Answered correctly

02 secs
Time Spent

05/04/2020
Last Updated

Explanation



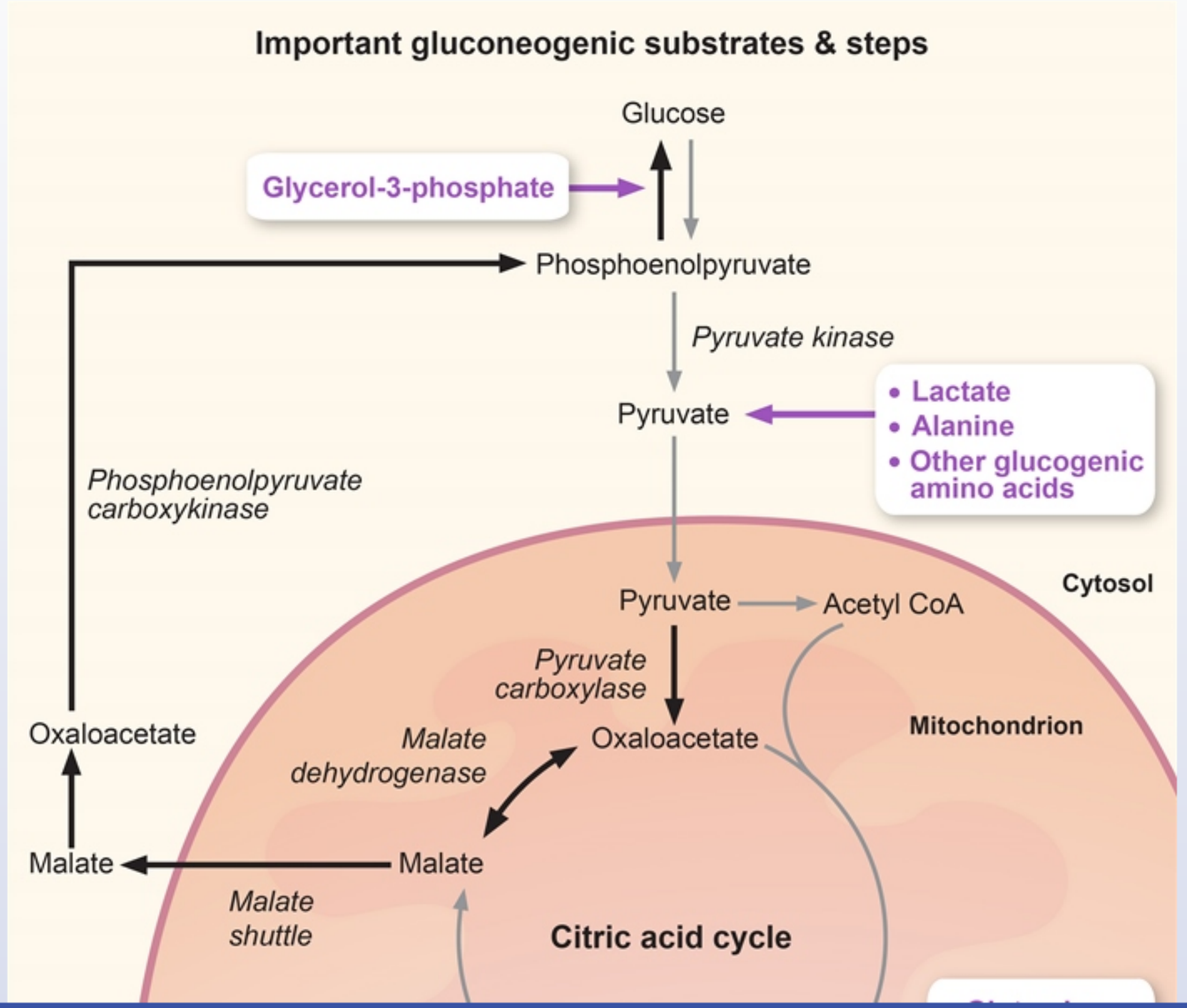
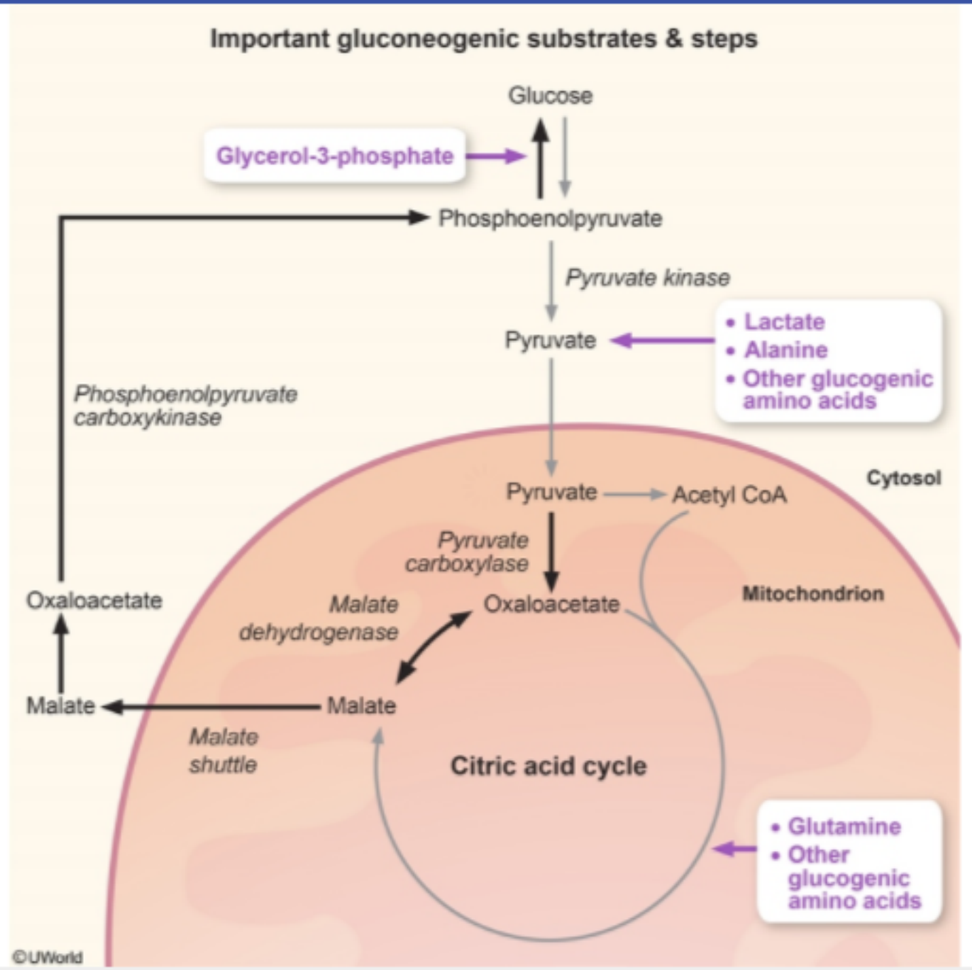

Important gluconeogenic substrates & steps
Glucose
Glycerol-3-phosphate
Phosphoenolpyruvate
Pyruvate kinase
Pyruvate
• Lactate
• Alanine
• Other glucogenic amino acids
Phosphoenolpyruvate carboxykinase
Cytosol
Pyruvate
Acetyl CoA
Pyruvate carboxylase
Oxaloacetate
Mitochondrion
Oxaloacetate
Malate dehydrogenase
Malate
Malate
Malate shuttle
Citric acid cycle

Exhibit Display



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The 2 major processes that maintain plasma glucose between meals are glycogenolysis and gluconeogenesis. Glycogenolysis is the primary source of glucose for the first 12-18 hours of fasting. Once hepatic glycogen stores become depleted, **gluconeogenesis** becomes the major process used by the body to keep blood glucose levels within the normal range. During gluconeogenesis, glucose is formed from lactate, glycerol, and glucogenic amino acids. This process uses many of the enzymes involved in glycolysis. However, hexokinase, phosphofructokinase, and pyruvate kinase are unidirectional and must be **bypassed** by distinct gluconeogenic enzymes.

The first committed step of gluconeogenesis is the biotin-dependent carboxylation of pyruvate to oxaloacetate by mitochondrial **pyruvate carboxylase**. Oxaloacetate is subsequently converted to malate by malate dehydrogenase to facilitate exit from the mitochondria, and then is converted back to oxaloacetate by cytosolic malate dehydrogenase (malate shuttle). In the cytosol, **phosphoenolpyruvate carboxykinase** (PEPCK) converts oxaloacetate to phosphoenolpyruvate. Therefore, pyruvate carboxylase and PEPCK work together to bypass pyruvate kinase. The 2 other unique gluconeogenic enzymes are **fructose 1,6-bisphosphatase** (bypasses phosphofructokinase) and **glucose-6-phosphatase** (bypasses hexokinase).

(Choice A) Conversion of acetoacetyl-CoA to 3-hydroxy-3-methylglutaryl-CoA occurs during the synthesis of cholesterol and ketone bodies. Ketone body synthesis is increased in starvation situations, however, ketone bodies cannot be used to synthesize glucose.

(Choice B) Palmitic acid is the first fatty acid produced from acetyl CoA during lipogenesis in the fed state. However, during prolonged fasting, lipolysis predominates and leads to generation of glycerol and fatty acids.

(Choice C) Conversion of fructose 6-phosphate to fructose 1,6-bisphosphate occurs during glycolysis and is catalyzed by phosphofructokinase. During starvation, glycolysis is minimized and gluconeogenesis predominates.

(Choice D) The first step of glycogenolysis is breakage of 1-4 glycosidic linkage to form glucose-1-phosphate. After 24 hours of fasting, maintenance of blood glucose levels is achieved mostly through gluconeogenesis, not by glycogenolysis.

Educational objective:
After 12-18 hours of fasting, gluconeogenesis becomes the principal source of blood glucose. Gluconeogenesis uses many glycolytic enzymes, but hexokinase, phosphofructokinase, and pyruvate kinase need to be bypassed as they are unidirectional. The initial steps of gluconeogenesis involve the conversion of pyruvate to oxaloacetate and oxaloacetate to phosphoenolpyruvate by pyruvate carboxylase and phosphoenolpyruvate carboxykinase, respectively.

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Biochemistry	Endocrine, Diabetes & Metabolism	Gluconeogenesis
Subject	System	Topic

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A 69-year-old woman with Alzheimer disease is brought to the emergency department after getting lost while taking a walk in her neighborhood. Her son has been unable to contact the patient for the last 2 days, and today the police found her wandering in a park. The patient says that she drank water from a park fountain but has not had anything to eat for over 24 hours. On physical examination, she is mildly confused with dry mucous membranes. Laboratory studies show a blood glucose level of 92 mg/dL. Which of the following hormones binds to an intracellular receptor to help maintain this patient's laboratory findings within the normal range?

- A. Cortisol
- B. Epinephrine
- C. Glucagon
- D. Growth hormone
- E. Insulin
- F. Norepinephrine

Submit

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- ✓ A. Cortisol (64%)
- B. Epinephrine (3%)
- C. Glucagon (26%)
- D. Growth hormone (2%)
- E. Insulin (2%)
- F. Norepinephrine (0%)

Omitted
Correct answer
A

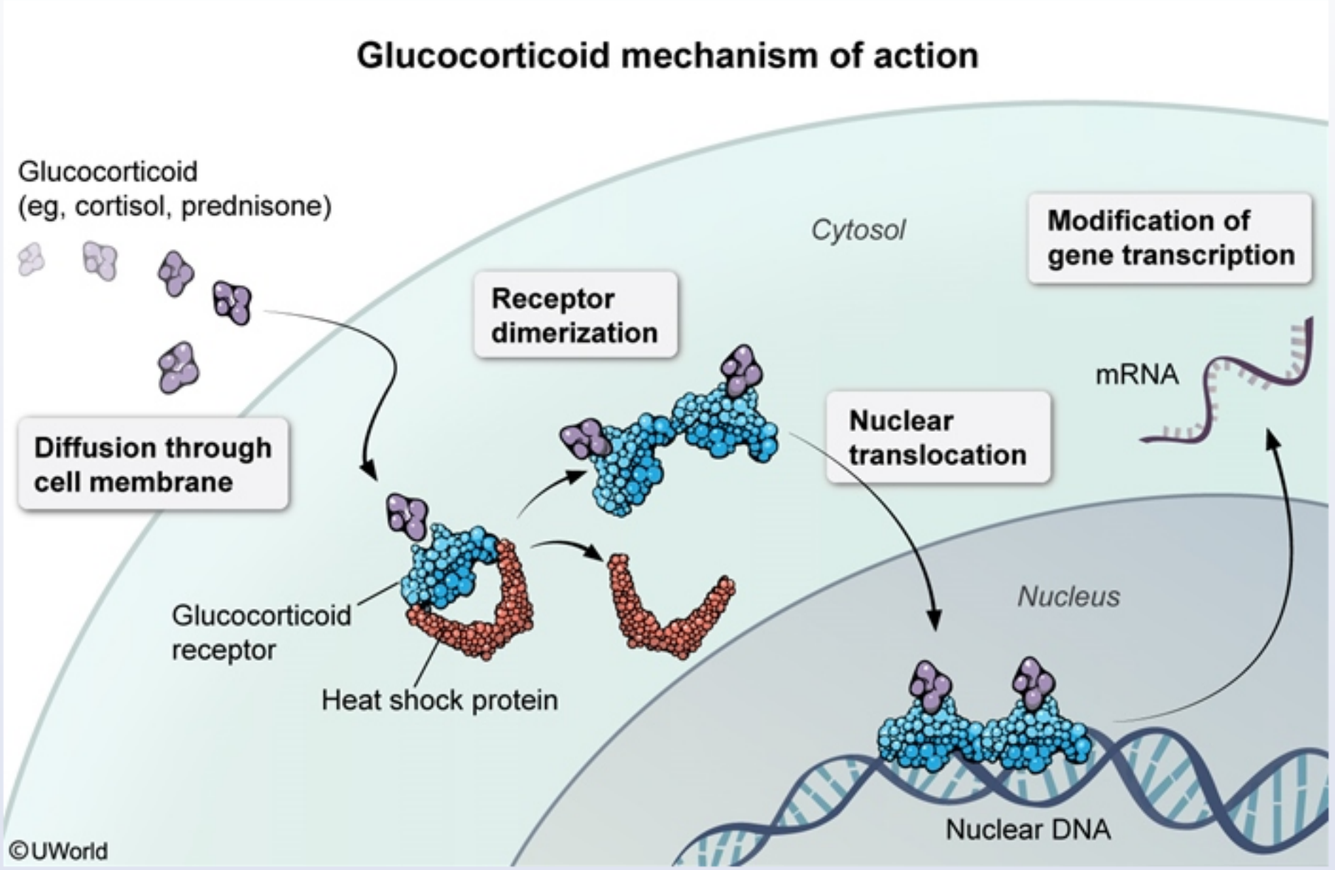
64%
Answered correctly

16 secs
Time Spent

06/09/2020
Last Updated

Explanation

Glucocorticoid mechanism of action



This patient has experienced a prolonged fast, but her blood glucose level is normal. As blood glucose levels fall in the fasting state, hypoglycemia is prevented due to suppression of insulin secretion and activation of counterregulatory hormones. **Glucagon** is the primary hormone secreted acutely in response to falling glucose levels; it stimulates hepatic glycogenolysis and gluconeogenesis. Concurrently, **epinephrine** further stimulates glycogenolysis and gluconeogenesis, increases the release of gluconeogenic substrates from muscle and fat, and limits glucose utilization by some insulin-sensitive peripheral tissues.

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As the fast continues, secretion of cortisol and growth hormone increases; these hormones attenuate hypoglycemia by altering transcription of key enzymes. In the inactivated state, **intracellular cortisol receptors** are found in the **cytoplasm** in association with heat shock proteins. Binding of cortisol to the carboxy terminal portion of the receptor causes the release of the heat shock proteins and allows receptor dimerization. The activated homodimers are then **transported to the nucleus**, where they control gene expression by binding to hormone-responsive DNA elements in the promoter region of target genes. Cortisol **increases transcription** of **gluconeogenic enzymes** as well as those involved in lipolysis and proteolysis.

(Choices B, C, and F) Catecholamines (eg, epinephrine, norepinephrine) and glucagon attenuate hypoglycemia. However, they exert their metabolic effects via *extracellular*, transmembrane, G protein–coupled receptors that activate adenyl cyclase and increase cyclic AMP production.

(Choice D) Growth hormone acts via an *extracellular*, transmembrane receptor that activates a JAK-STAT pathway. Growth hormone antagonizes insulin action, increases gluconeogenesis, and promotes lipolysis (provides gluconeogenic substrates).

(Choice E) In addition to the production of counterregulatory hormones, the inhibition of insulin release from pancreatic beta cells plays a primary role in preventing hypoglycemia during fasting. However, insulin acts on a *extracellular* transmembrane receptor with intrinsic tyrosine kinase activity.

Educational objective:
In a fasting state, glucagon and epinephrine bind to transmembrane receptors and prevent hypoglycemia by increasing hepatic glycogenolysis and gluconeogenesis. Prolonged fasting increases the secretion of cortisol, a steroid hormone that binds to an intracellular receptor and acts to increase transcription of enzymes involved in gluconeogenesis, lipolysis, and proteolysis.

epinephrine further stimulates glycogenolysis and gluconeogenesis, increases the release of gluconeogenic substrates from muscle and fat, and limits glucose utilization by some insulin-sensitive peripheral tissues.

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Biochemistry	Endocrine, Diabetes & Metabolism	Gluconeogenesis
Subject	System	Topic

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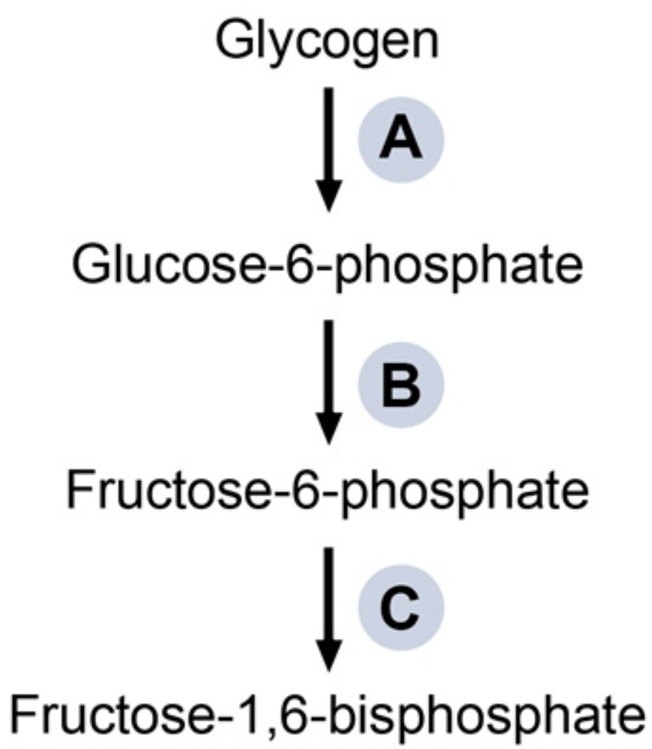
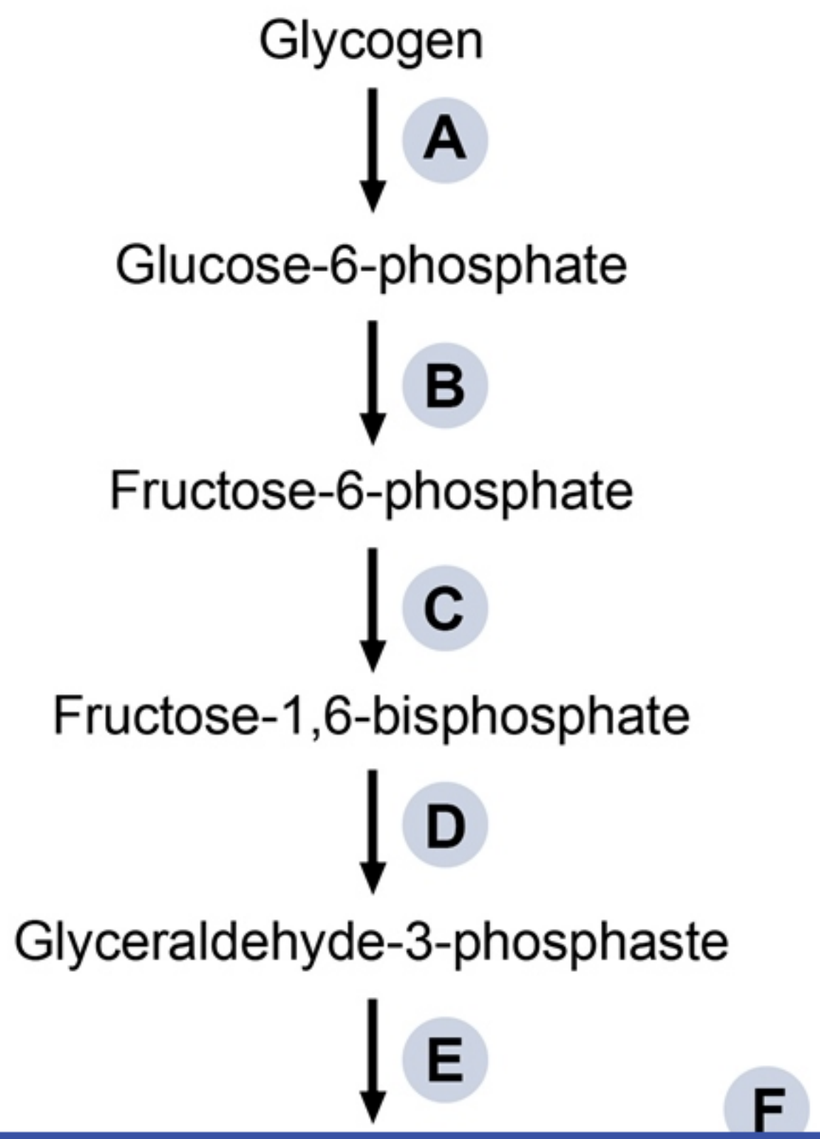
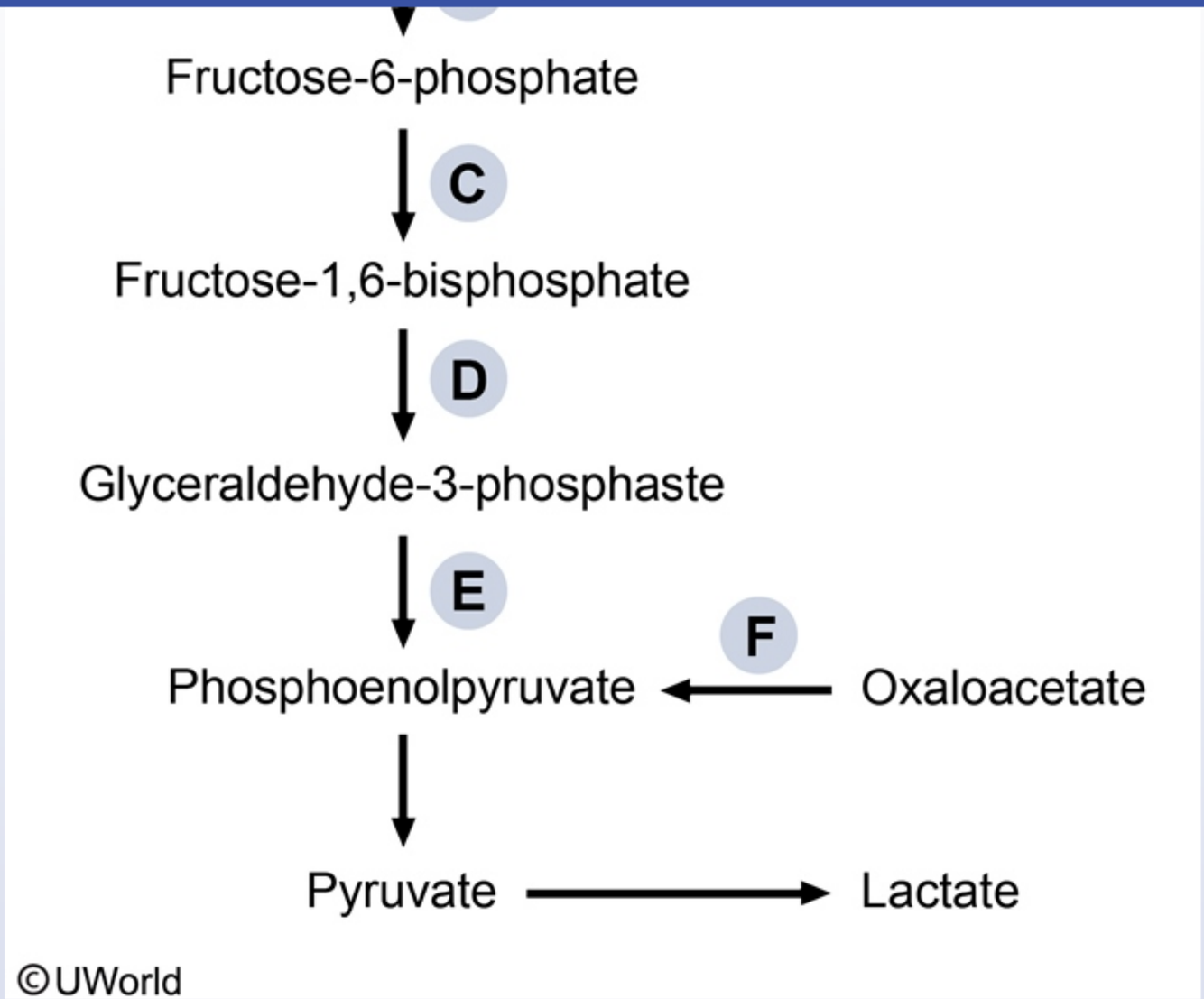
A 34-year-old woman is brought to the emergency department in the early morning with confusion, tremor, and sweating. Her husband reports that she did not wake to her alarm clock and was difficult to arouse. Over the past week, the patient has had similar episodes in the morning before eating and after exercise. Past medical history is unremarkable. Blood pressure is 135/95 mm Hg, pulse is 110/min, and respirations are 24/min. The patient is arousable to voice but does not follow commands. Cranial nerve examination, muscle tone, and deep tendon reflexes are normal. A bedside fingerstick glucose level is 35 mg/dL. The patient is given an intravenous infusion of glucose, which rapidly improves her mental status. Further evaluation reveals that her episodes of hypoglycemia are due to increased levels of an endogenous hormone. This hormonal imbalance is most likely causing the patient's symptoms by stimulating which of the following conversions?




Glycogen
A
Glucose-6-phosphate
B
Fructose-6-phosphate
C
Fructose-1,6-bisphosphate
D
Glyceraldehyde-3-phosphaste
E
F


Fructose-6-phosphate
C
Fructose-1,6-bisphosphate
D
Glyceraldehyde-3-phosphaste
E
F
Phosphoenolpyruvate
Oxaloacetate
Pyruvate
Lactate
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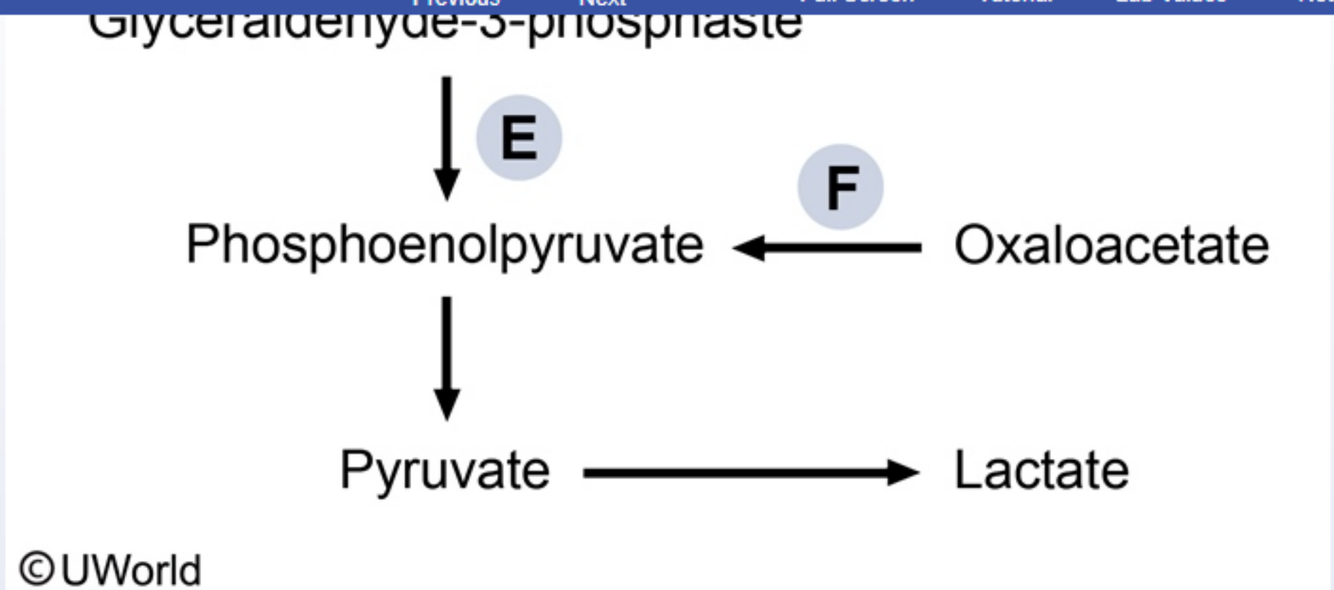
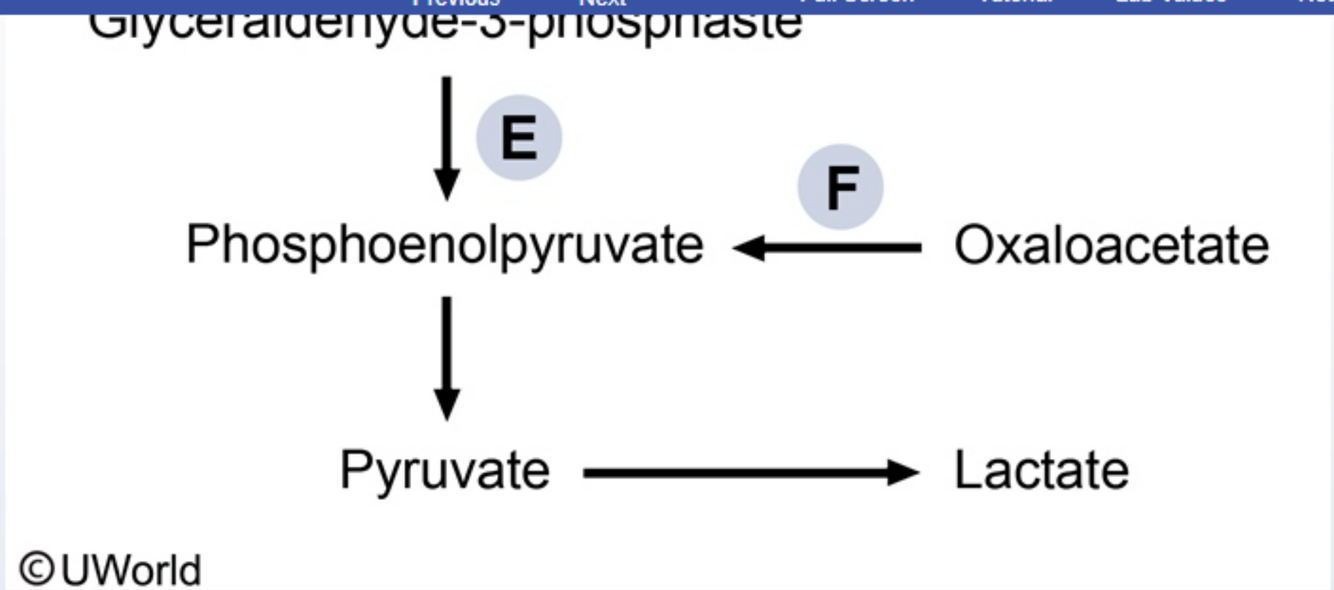
A. A



A. A
B. B
C. C
D. D
E. E
F. F

Submit



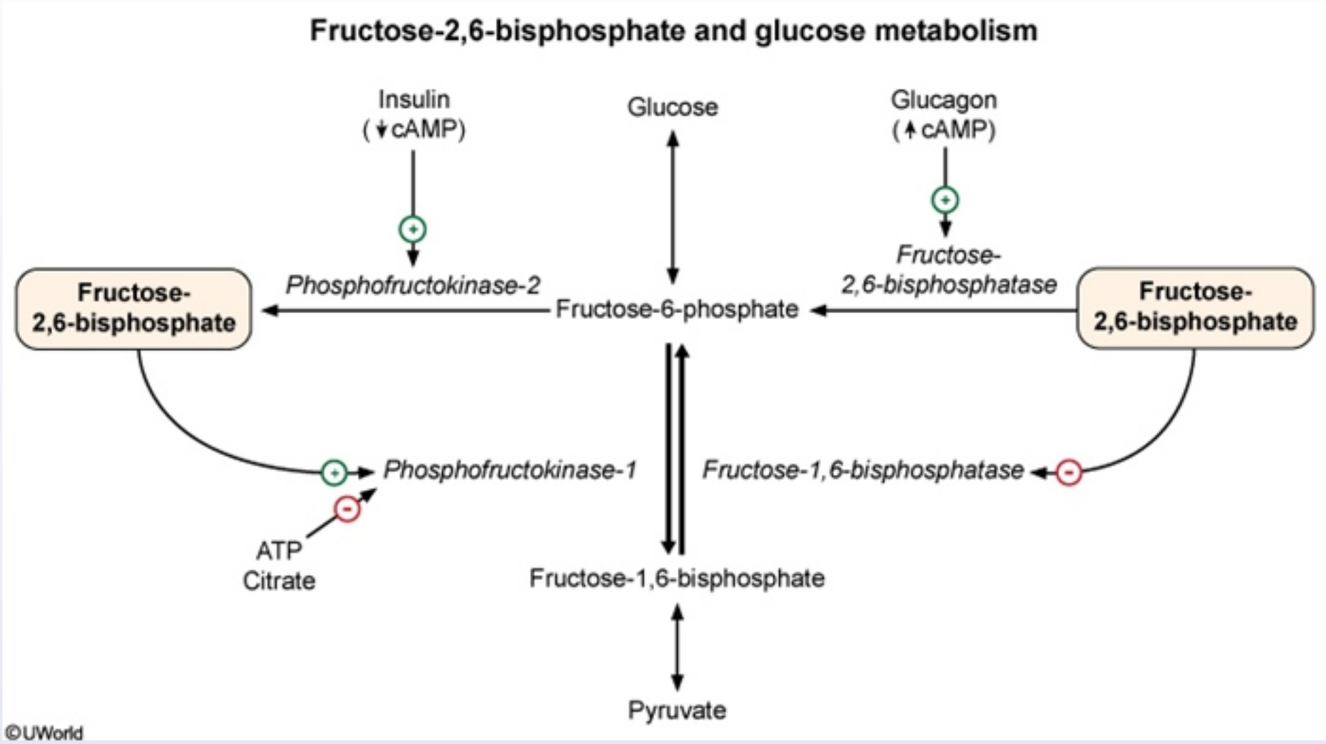
A. A (20%)
B. B (9%)
✓ C. C (43%)
D. D (5%)
E. E (3%)
F. F (18%)

Omitted
Correct answer

43%
Answered correctly

09 secs
Time Spent

04/27/2020
Last Updated



This patient has developed **hypoglycemia** secondary to **increased levels of an endogenous hormone**. Hypoglycemia can develop due to **insulin excess** (either endogenous [eg, insulinoma] or exogenous [eg, inadvertent overdose, surreptitious insulin/secretagogue use]) as well as deficiency of counterregulatory hormones (eg, glucagon, epinephrine, cortisol).

Insulin lowers plasma glucose by increasing glucose uptake in fat, muscle, and liver. In addition, insulin causes an **increase in glycolysis** by **activating** phosphofructokinase-2 (**PFK2**), the enzyme that produces fructose 2,6-bisphosphate. The intracellular concentration of fructose 2,6-bisphosphate is the major regulator of phosphofructokinase-1 (**PFK1**), which **converts fructose 6-phosphate** to **fructose 1,6-bisphosphate** in the rate-limiting step of glycolysis. Fructose 2,6-bisphosphate stimulates PFK1 while inhibiting the reverse enzyme, fructose 1,6-bisphosphatase. As a result, the rise in fructose 2,6-bisphosphate levels caused by insulin leads to an increase in glycolysis and inhibition of gluconeogenesis, with a corresponding **decrease** in circulating **glucose levels**.

Insulin excess (either endogenous [eg, insulinoma] or exogenous [eg, inadvertent overdose, surreptitious insulin/secretagogue use]) as well as deficiency of counterregulatory hormones (eg, glucagon, epinephrine, cortisol).

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(Choice A) Insulin promotes the storage of glucose by *inhibiting* glycogen phosphorylase (breaks down glycogen into glucose-6-phosphate) and stimulating glycogen synthase (incorporates UDP-glucose into glycogen).

(Choices B, D, and E) Glucose 6-phosphate is converted to fructose 6-phosphate by phosphoglucose isomerase. Fructose 1,6-bisphosphate is converted to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate by fructose bisphosphate aldolase. Glyceraldehyde 3-phosphate is converted to phosphoenolpyruvate through the action of multiple enzymes. These steps are readily reversible and not regulated by insulin.

(Choice F) Oxaloacetate is converted to phosphoenolpyruvate by phosphoenolpyruvate carboxykinase during gluconeogenesis; this reaction is *downregulated* by high insulin levels.

Educational objective:
Phosphofructokinase-1 (PFK1) catalyzes the rate-limiting step in glycolysis, and the most potent stimulator of PFK1 is fructose 2,6-bisphosphate. Insulin increases production of fructose 2,6-bisphosphate by phosphofructokinase-2 (PFK2), thereby stimulating glycolysis.

References

- Roles for fructose-2,6-bisphosphate in the control of fuel metabolism: beyond its allosteric effects on glycolytic and gluconeogenic enzymes.

Biochemistry	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

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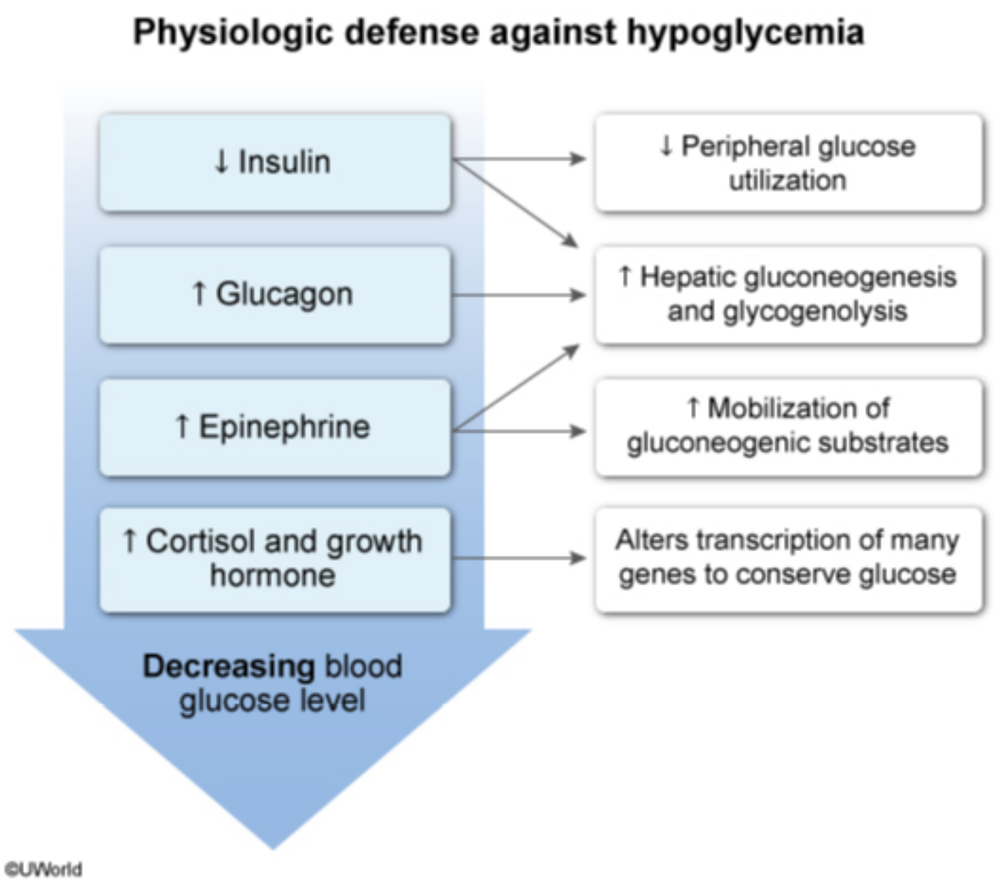
Exhibit Display



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A 45-year-old man is referred to an endocrinologist for newly diagnosed diabetes mellitus. A week ago, his primary care physician noted an elevated fasting serum glucose level. The endocrinologist discusses the different treatment options available, including oral and injectable medications. He recommends treatment with a medication that alters glucose metabolism within the liver by increasing the concentration of fructose 2,6-bisphosphate within hepatocytes. Which of the following conversions will be inhibited by high intracellular concentrations of this metabolite?

- A. Acetyl CoA → fatty acids
- B. Alanine → glucose
- C. Fructose-6-phosphate → fructose-1,6-bisphosphate
- D. Glucose → glycogen
- E. NAD^+ → NADH

Submit

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- A. Acetyl CoA → fatty acids (3%)
- ✓ B. Alanine → glucose (37%)
- C. Fructose-6-phosphate → fructose-1,6-bisphosphate (43%)
- D. Glucose → glycogen (10%)
- E. NAD^+ → NADH (5%)

Omitted
Correct answer
B

37%
Answered correctly

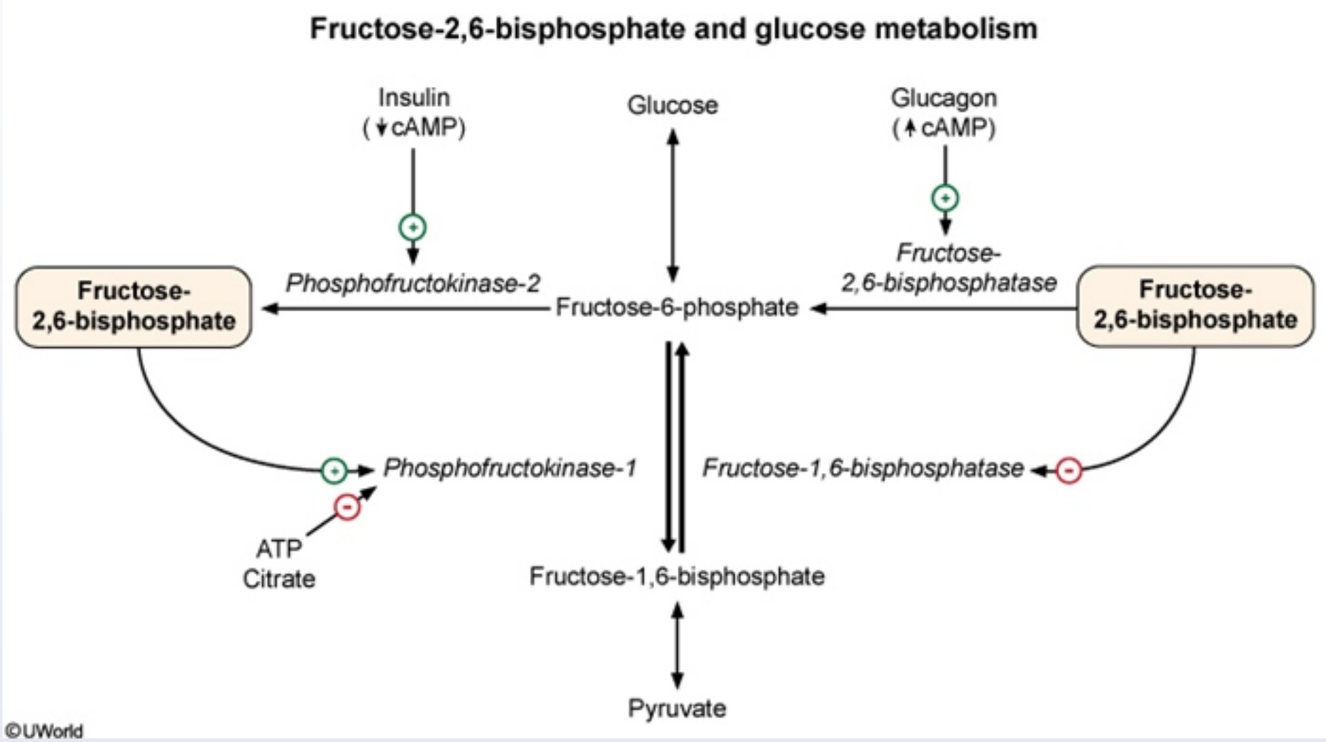
02 secs
Time Spent

04/29/2020
Last Updated

Explanation

Fructose-2,6-bisphosphate and glucose metabolism

Insulin (↓cAMP) | Glucose | Glucagon (↑cAMP)



Fructose 2,6-bisphosphate helps control the balance between **gluconeogenesis** and **glycolysis** through inverse regulation of phosphofructokinase-1 (PFK-1) and fructose 1,6-bisphosphatase. Fructose 2,6-bisphosphate activates PFK-1, the main regulatory enzyme involved in glycolysis, which converts fructose 6-phosphate to fructose 1,6-bisphosphate. The opposite reaction (fructose 1,6-bisphosphate to fructose-6-phosphate) occurs in gluconeogenesis and is catalyzed by the enzyme fructose-1,6-bisphosphatase (inhibited by fructose 2,6-bisphosphate).

The interconversion of fructose-6-phosphate and fructose 2,6-bisphosphate is achieved by a bifunctional enzyme complex composed of PFK-2 (increases fructose 2,6-bisphosphate levels) and fructose 2,6-bisphosphophosphatase (decreases fructose 2,6-bisphosphate levels). **Insulin** causes activation of PFK-2, leading to **increased fructose 2,6-bisphosphate levels** and **augmented glycolysis**. High concentrations of fructose 2,6-bisphosphate also **inhibit gluconeogenesis**, leading to **decreased conversion of alanine** and other gluconeogenic substrates to glucose.

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(Choice A) Fatty acid synthesis is upregulated by insulin and high citrate levels (which increase when acetyl-CoA is abundant, as with active glycolysis). Therefore, fatty acid synthesis is likely to be upregulated in metabolic states in which fructose 2,6-bisphosphate concentration is increased.

(Choice C) The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate is catalyzed by the enzyme PFK-1. This enzyme is allosterically activated by high levels of fructose-2,6-bisphosphate, and so conversion would be increased.

(Choice D) Glycogen formation is stimulated by increased levels of insulin and glucose-6-phosphate. Because elevated insulin levels also increase fructose 2,6-bisphosphate formation, the rise of fructose 2,6-bisphosphate levels in hepatocytes is typically concurrent with increased glycogen synthesis.

(Choice E) The rise in fructose-2,6-bisphosphate accelerates glycolysis, leading to increased conversion of NAD^+ to NADH.

Educational objective:
Fructose 2,6-bisphosphate (F2,6BP) activates phosphofructokinase-1 (increasing glycolysis) and inhibits fructose 1,6-bisphosphatase (decreasing gluconeogenesis). F2,6BP concentration is regulated by a bifunctional enzyme complex: phosphofructokinase-2 increases F2,6BP levels in response to insulin, and fructose 2,6-bisphosphatase decreases F2,6BP levels in response to glucagon.

References

- Glucagon and regulation of glucose metabolism.

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References

- Glucagon and regulation of glucose metabolism.
- Elucidation of the role of fructose 2,6-bisphosphate in the regulation of glucose fluxes in mice using in vivo (13)C NMR measurements of hepatic carbohydrate metabolism.

Biochemistry	Endocrine, Diabetes & Metabolism	Fructose 2 6 biphosphate
Subject	System	Topic

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A 6-month-old full-term boy is brought to the emergency department with lethargy and vomiting. He was born by uncomplicated spontaneous vaginal delivery and has been growing and developing normally. The patient was breastfed exclusively until 2 days ago when homemade pureed food was added to his diet. He has had no fever or diarrhea. His parents are healthy and he has had no sick contacts. Examination shows a pale, diaphoretic, and ill-appearing infant. Serum glucose is 30 mg/dL. Diagnostic testing confirms aldolase B deficiency. Which of the following should be removed from this patient's diet?

- A. Amylose
- B. Cellulose
- C. Galactose
- D. Glucose
- E. Lactose
- F. Maltose
- G. Sucrose

Submit

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- A. Amylose (1%)
- B. Cellulose (1%)
- C. Galactose (16%)
- D. Glucose (1%)
- E. Lactose (4%)
- F. Maltose (4%)
- ✓ G. Sucrose (71%)

Omitted
Correct answer
G

71%
Answered correctly

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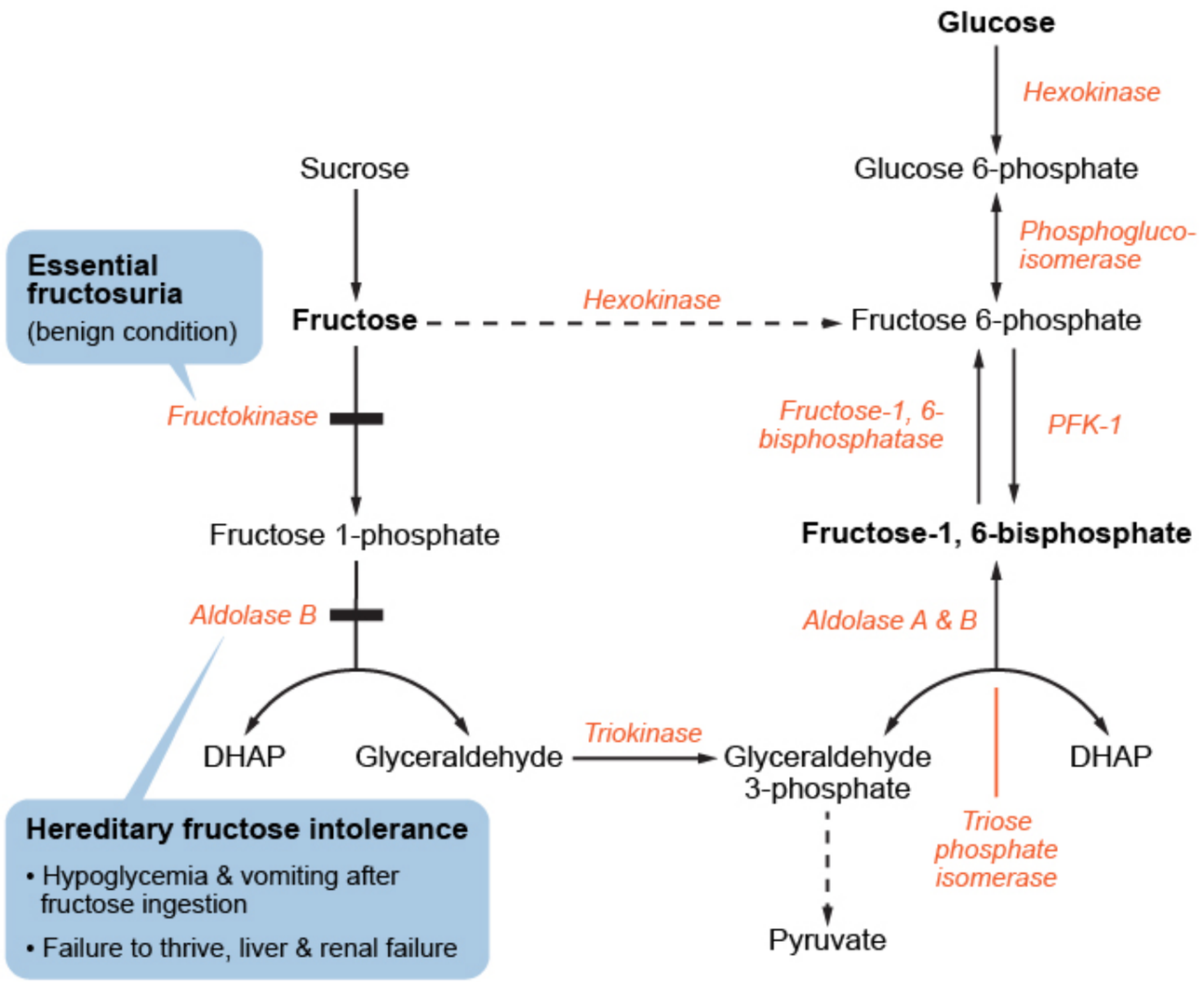
03/23/2020
Last Updated

Explanation

Disorders of fructose metabolism

Disorders of fructose metabolism



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Carbohydrates are classified as monosaccharides, disaccharides, and polysaccharides. Disaccharides and polysaccharides must be broken down to their monosaccharide components for energy production and utilization.

Aldolase B metabolizes fructose-1-phosphate, a product of fructose metabolism, to dihydroxyacetone phosphate (DHAP) and glyceraldehyde, which can then enter the glycolytic pathway. Aldolase B deficiency can result in **fructose-1-phosphate accumulation**; this toxic metabolite depletes intracellular phosphate and inhibits the activation of hepatic phosphorylase and gluconeogenesis. The resulting condition, hereditary fructose intolerance (eg, fructosemia), is an **autosomal recessive** disorder.

Because **gluconeogenesis is impaired**, fructosemia typically presents with life-threatening **hypoglycemia**. Consequences of hypoglycemia include lethargy, sweating, vomiting, and dehydration. These symptoms manifest after intake of fructose or sucrose, such as from formula or fruit. Strict abstinence from **dietary fructose and sucrose** can result in dramatic recovery.

(Choices A and D) Starch (similar to glycogen in mammals) is the major storage form of carbohydrates in plants and contains only glucose molecules. Starch consists of an unbranched portion composed of amylose and a branched portion called amylopectin. Patients with fructosemia have normal metabolism of glucose.

(Choice B) Cellulose is a linear polysaccharide of glucose that is mainly present in the cell wall of plant cells. Cellulose is an insoluble, indigestible dietary fiber that is responsible for the bulk of fecal matter.

(Choices C, E, and F) Breast milk contains the disaccharides lactose (composed of galactose and glucose) and maltose (composed of 2 glucose molecules). Patients with aldolase B deficiency can consume these disaccharides as their breakdown will not produce fructose. However, patients with galactosemia cannot metabolize galactose in breast milk or cow's milk-based formula. These patients typically present in the first few days of life with jaundice, vomiting, poor feeding, and hepatomegaly.

Educational objective:
Aldolase B deficiency, or hereditary fructose intolerance, leads to accumulation of the toxic metabolite fructose-1-phosphate. Patients have hypoglycemia and vomiting when fructose or sucrose is consumed. Treatment involves strict removal of both carbohydrates from the diet.

References

- Inborn errors of carbohydrate metabolism.

Because **gluconeogenesis is impaired**, fructosemia typically presents with life-threatening **hypoglycemia**. Consequences of hypoglycemia include lethargy, sweating, vomiting, and dehydration. These symptoms manifest after intake of fructose or sucrose, such as from formula or fruit. Strict abstinence from **dietary fructose and sucrose** can result in dramatic recovery.

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Aldolase B deficiency, or hereditary fructose intolerance, leads to accumulation of the toxic metabolite fructose-1-phosphate. Patients have hypoglycemia and vomiting when fructose or sucrose is consumed. Treatment involves strict removal of both carbohydrates from the diet.

References

- Inborn errors of carbohydrate metabolism.
- The biochemical basis of hereditary fructose intolerance.

Biochemistry	Endocrine, Diabetes & Metabolism	Fructose metabolism
Subject	System	Topic

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A 5-month-old boy is brought to the office due to poor feeding. His mother says that he has difficulty holding his head up while breastfeeding and his suckling seems weaker than it used to be. His current weight is between the 5th-10th percentile, and length and head circumference are tracking along the 25th percentile. Physical examination shows hepatomegaly and hypotonia in all 4 limbs. Cardiac auscultation reveals a gallop rhythm, and chest x-ray shows severe cardiomegaly. Muscle biopsy shows enlarged lysosomes containing periodic acid-Schiff (PAS)-positive material. Which of the following enzymes is most likely deficient in this patient?

- A. Acid α-glucosidase
- B. Debrancher enzyme
- C. Galactokinase
- D. Glucose-6-phosphatase
- E. Glycogen phosphorylase
- F. Pyruvate kinase

Submit

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- ✓ A. Acid α-glucosidase (56%)
- B. Debrancher enzyme (14%)
- C. Galactokinase (4%)
- D. Glucose-6-phosphatase (8%)
- E. Glycogen phosphorylase (12%)
- F. Pyruvate kinase (2%)

Omitted
Correct answer
A

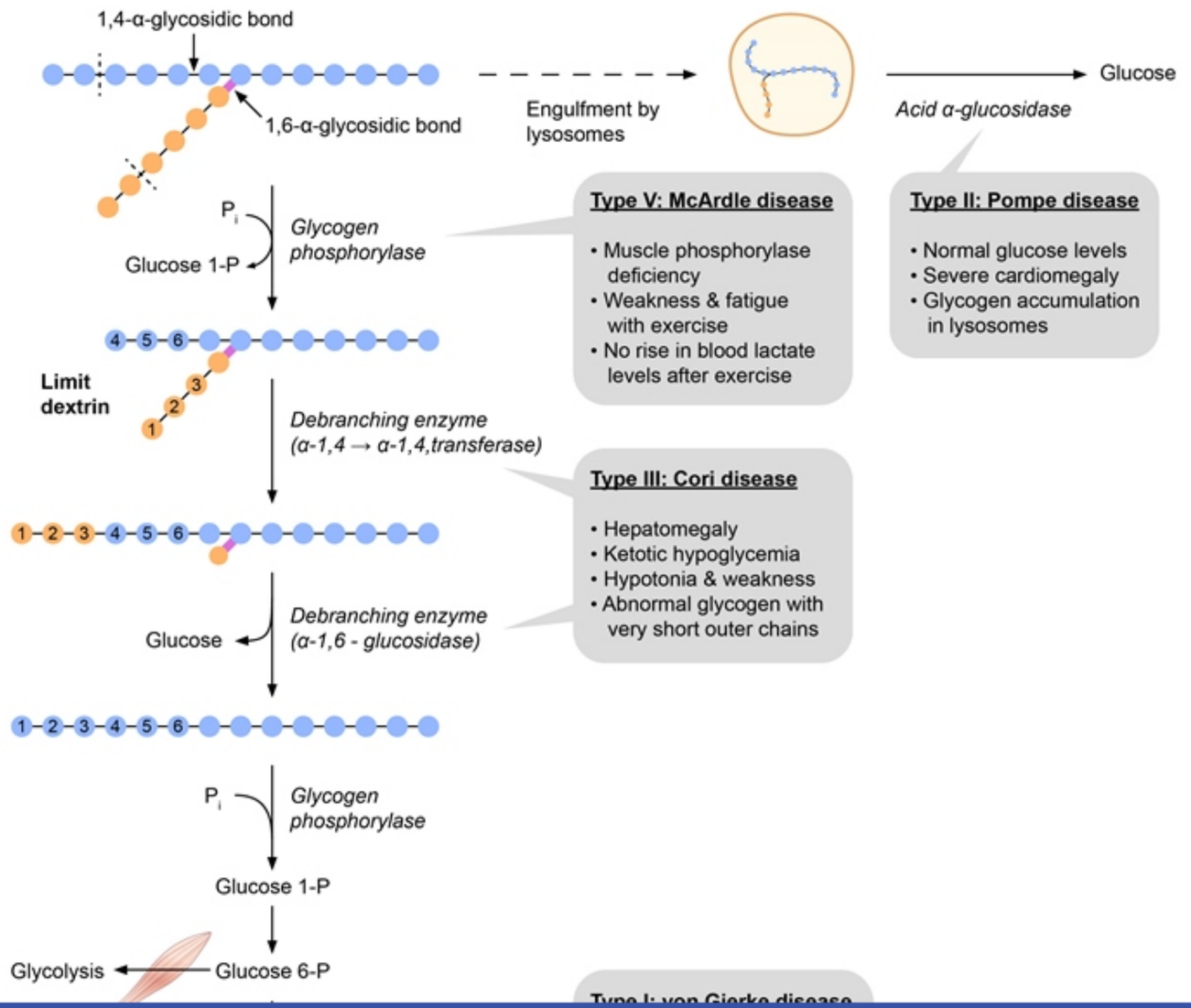
56%
Answered correctly

02 secs
Time Spent

05/10/2020
Last Updated

Explanation

Impairments in glycogenolysis



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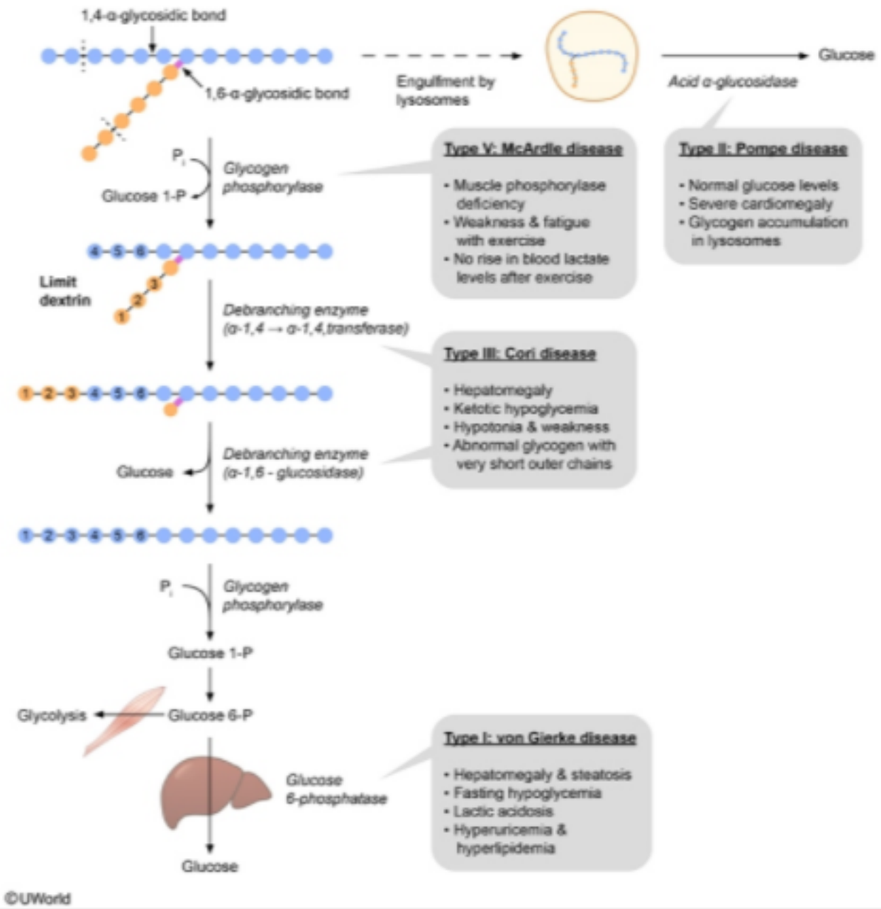
Impairments in glycogenolysis



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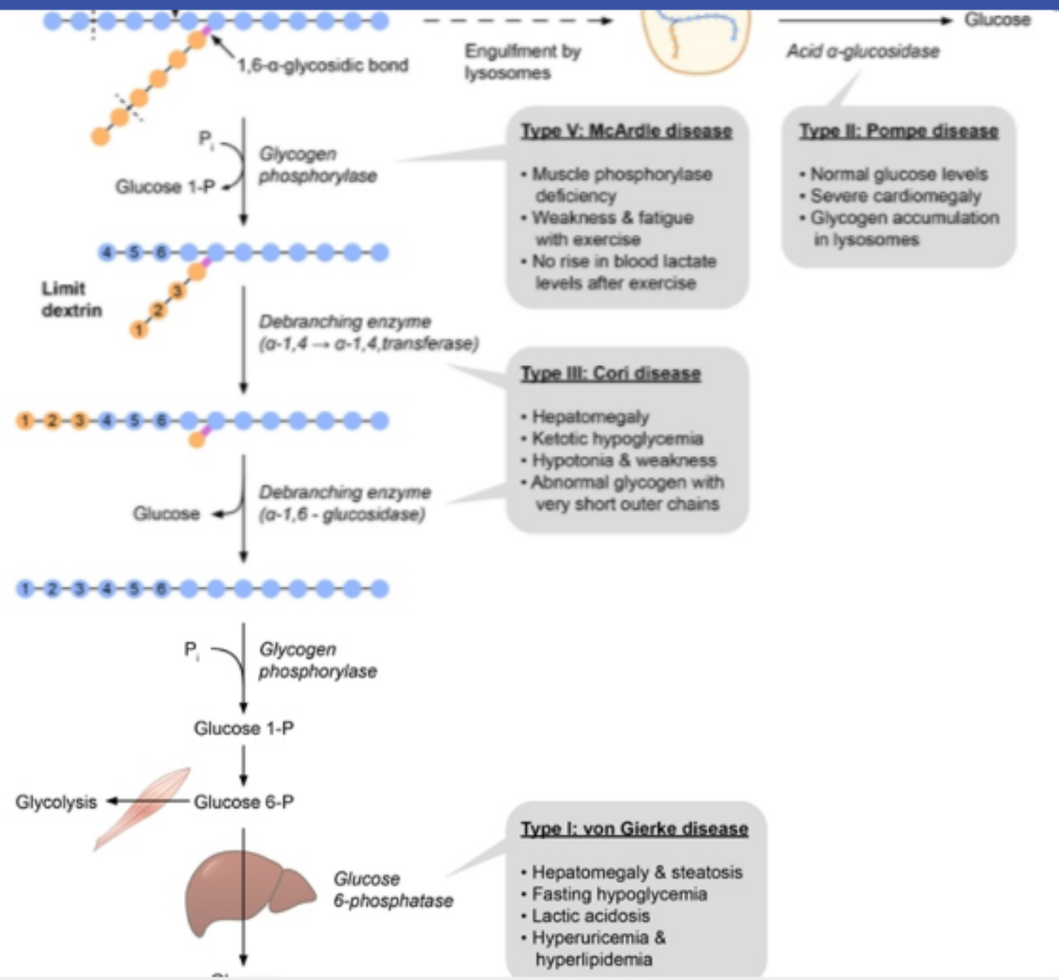

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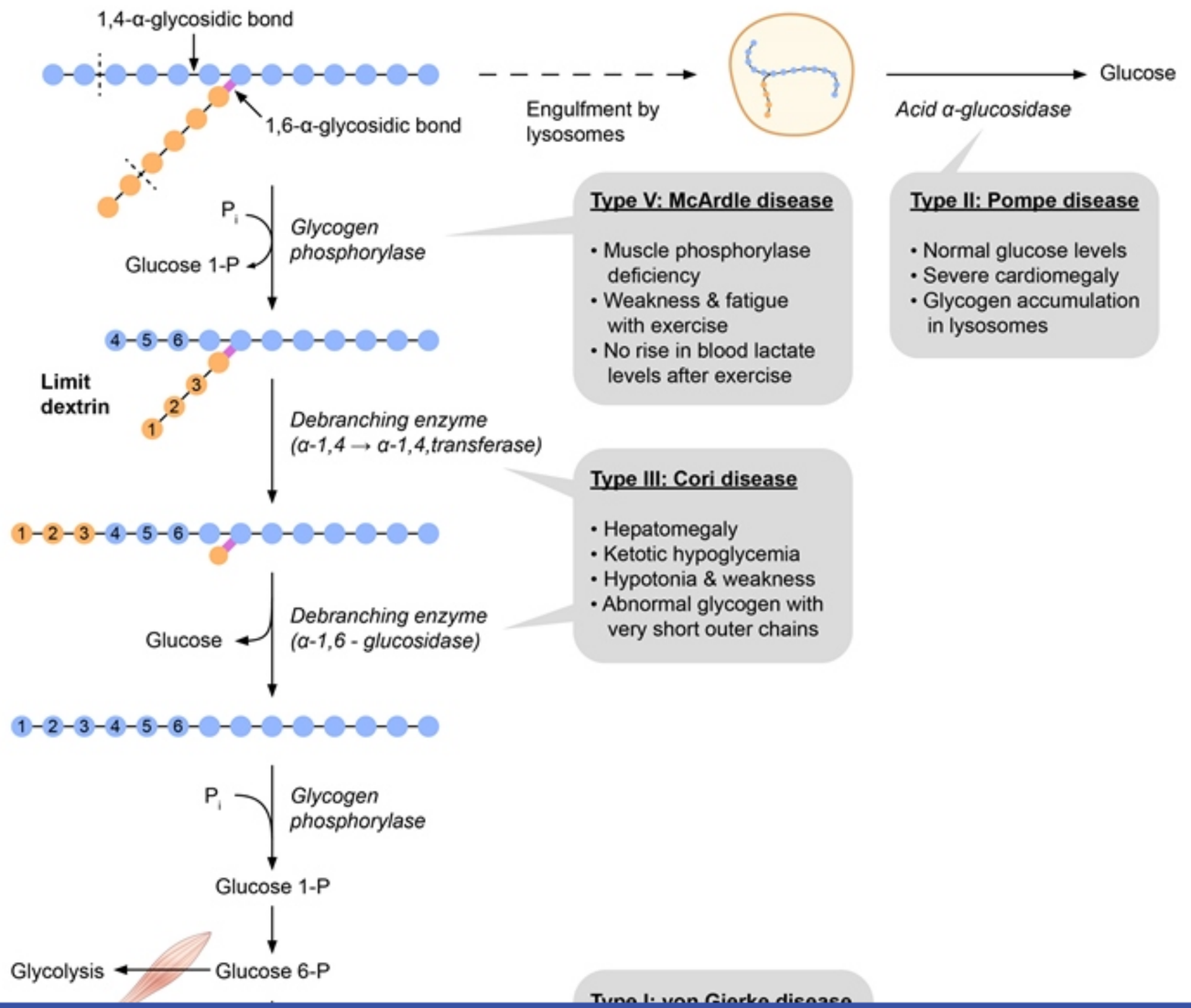
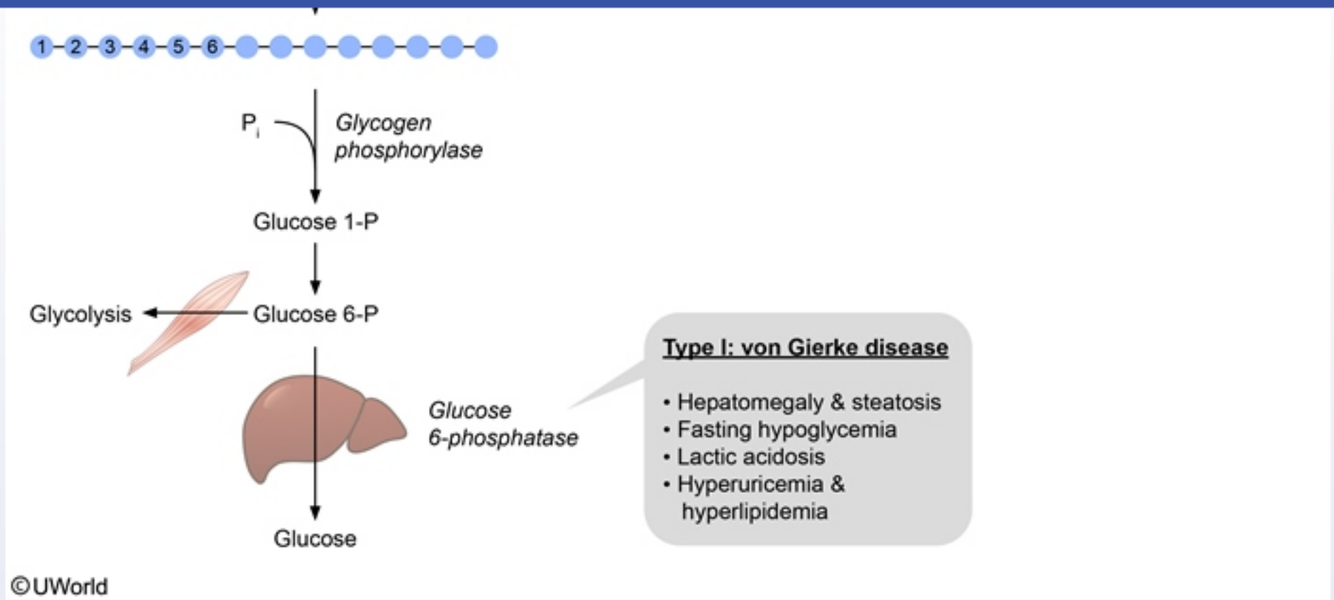
Impairments in glycogenolysis





This patient most likely has glycogen storage disease type II (**Pompe disease**). This condition is caused by deficiency of **acid α-glucosidase** (acid maltase), an enzyme responsible for breaking down glycogen within the acidic environment of lysosomes. Although most glycogen is degraded in the cytoplasm, a small amount is inadvertently engulfed by lysosomes, especially in cells containing high amounts of glycogen such as hepatocytes and myocytes. As such, deficiency of acid maltase results in pathologic accumulation of glycogen within liver and muscle lysosomes. Cardiac and skeletal muscle are particularly susceptible, as the ballooning lysosomes interfere with contractile function.

The classic form of the disease presents in early infancy with marked **cardiomegaly**, severe generalized **hypotonia**, macroglossia, and hepatomegaly. Blood glucose levels are normal, unlike with glycogen storage diseases that primarily affect the liver (eg, von Gierke). A key distinguishing feature is that muscle biopsy will show accumulation of **glycogen in lysosomes**.

(Choices B, D, and E) Other glycogen storage diseases are caused by deficiencies of glucose-6-phosphatase, glycogen phosphorylase, and debrancher enzyme. However, glycogen accumulation within lysosomal vacuoles is specific for acid α-glucosidase deficiency.

(Choice C) Galactokinase catalyzes the phosphorylation of galactose to galactose-1-phosphate in the first committed step of galactose catabolism. Galactokinase deficiency causes neonatal cataract formation due to accumulation of galactitol in the lens.

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(Choice C) Galactokinase catalyzes the phosphorylation of galactose to galactose-1-phosphate in the first committed step of galactose catabolism. Galactokinase deficiency causes neonatal cataract formation due to accumulation of galactitol in the lens.

(Choice F) Pyruvate kinase deficiency causes chronic hemolytic anemia, splenomegaly, and iron overload as a result of impaired erythrocyte survival.

Educational objective:
Acid maltase (α-glucosidase) deficiency presents in early infancy with cardiomegaly, macroglossia, and profound muscular hypotonia. Abnormal glycogen accumulation within lysosomal vesicles is seen on muscle biopsy.

References

- Lysosomal dysfunction in muscle with special reference to glycogen storage disease type II.

Biochemistry	Endocrine, Diabetes & Metabolism	Glycogen storage disease
Subject	System	Topic

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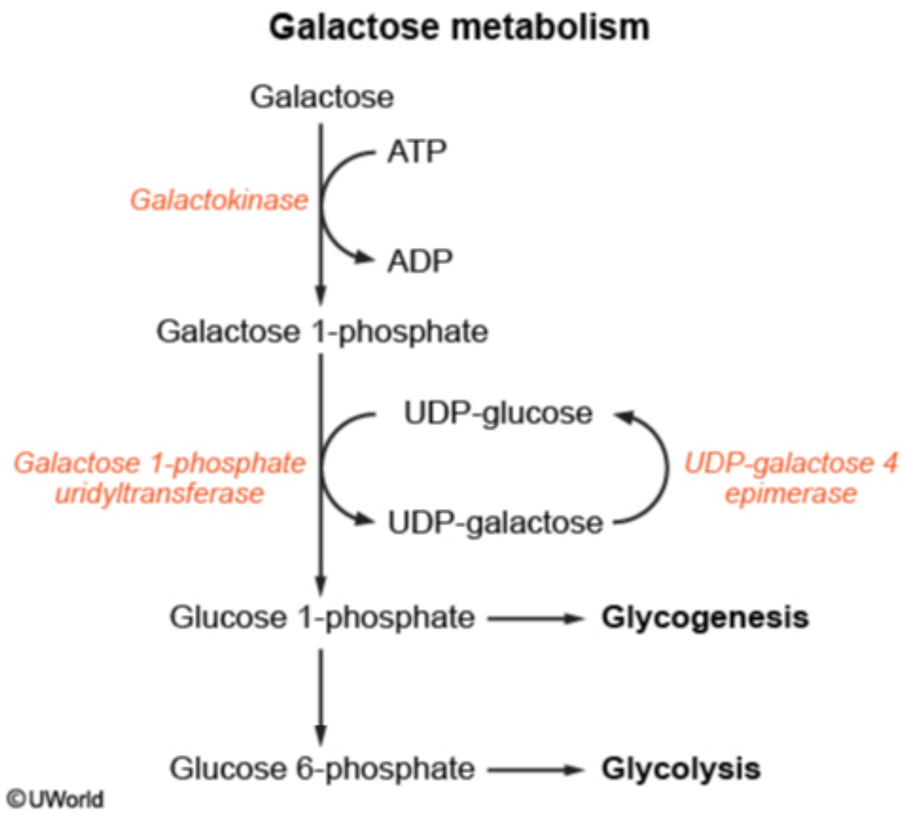
This patient most likely has glycogen storage disease type II (**Pompe disease**). This condition is caused by deficiency of **acid α-glucosidase**

Exhibit Display



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A 72-year-old woman is brought to the emergency department after lying on the floor in her home for the past 2 days. The patient's neighbor called police after phone calls were not answered and no one opened the door. She was found awake on the bathroom floor lying in feces and urine. The patient says she fell and injured her right hip and was unable to get up to call for help. She did not eat or drink anything during that time. On examination, the patient appears dehydrated and has right hip tenderness. Laboratory studies show serum glucose of 72 mg/dL and positive urine ketones. Radiographs of the right hip show a right femoral neck fracture. Increased activity of which of the following enzymes is most likely contributing to both the serum and urine laboratory findings?

- A. Glycogen phosphorylase
- B. Hormone-sensitive lipase
- C. Lipoprotein lipase
- D. Mitochondrial HMG CoA synthase
- E. Phosphofructokinase-1

Submit

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- A. Glycogen phosphorylase (17%)
- ✓ B. Hormone-sensitive lipase (40%)
- C. Lipoprotein lipase (11%)
- D. Mitochondrial HMG CoA synthase (20%)
- E. Phosphofructokinase-1 (10%)

Omitted
Correct answer
B

40%
Answered correctly

02 secs
Time Spent

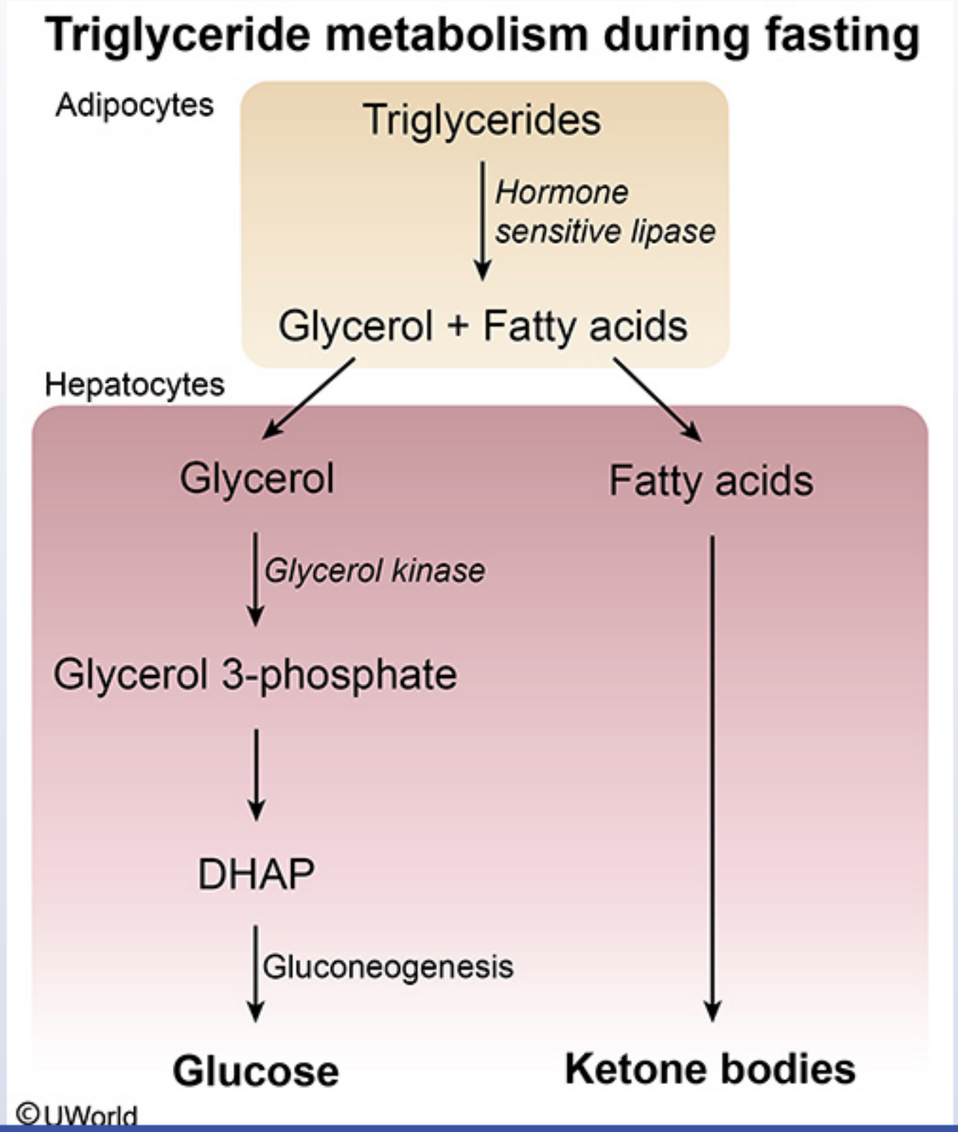
06/14/2020
Last Updated

Explanation

Triglyceride metabolism during fasting

Adipocytes

Triglycerides


Triglyceride metabolism during fasting
Adipocytes
Triglycerides
Hormone sensitive lipase
Glycerol + Fatty acids
Hepatocytes
Glycerol
Fatty acids
Glycerol kinase
Glycerol 3-phosphate
DHAP
Gluconeogenesis
Glucose
Ketone bodies
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This patient's laboratory studies show the presence of ketones in the urine and maintenance of fasting blood glucose values in the low-normal range despite prolonged fasting.

Hormone-sensitive lipase (HSL) is an enzyme found in adipose tissue that catalyzes the mobilization of stored triglycerides into **free fatty acids** (FFAs) and **glycerol**. HSL is activated in response to stress hormones (eg, catecholamines, glucagon, ACTH), whereas it is inhibited by the release of insulin. The stress hormones stimulate Gs protein-coupled receptors on adipocytes, leading to increased cAMP production and activation of protein kinase A (PKA). Finally, PKA phosphorylates and activates HSL, stimulating lipolysis.

FFAs and glycerol released into the circulation can be taken up by the liver, where the glycerol is used primarily as a carbon source for **gluconeogenesis**. The liver oxidizes the FFAs to acetyl-coA, which can then be further metabolized to **ketone bodies** (eg, acetoacetate, beta-hydroxybutyrate) or shunted into the TCA cycle to generate energy for gluconeogenesis. During starvation, most tissues utilize a combination of FFAs and ketones for their energy needs. Important exceptions include the brain (FFAs do not cross the blood-brain barrier, so only ketone bodies/glucose can be used) and erythrocytes (can use only glucose due to lack of mitochondria).

(Choice A) Glycogen phosphorylase is the rate-limiting enzyme in glycogenolysis, a process that frees glucose-1-phosphate from stored glycogen chains. Glycogenolysis increases blood glucose levels during the first several hours of fasting but has no effect on fatty acid oxidation.

(Choice C) Lipoprotein lipase is an enzyme found on endothelial cells that functions to degrade triglycerides found in chylomicrons and VLDL. Although it is functionally similar to HSL, it works in the bloodstream to form FFAs that are then transported into adipocytes storage or used by tissues (eg, heart/skeletal muscle) for energy production.

(Choice D) Mitochondrial HMG-CoA synthase plays a role in the production of ketones. Although it could be responsible for the presence of urinary ketone bodies in this patient, it would not account for the maintenance of blood glucose levels.

(Choice E) Phosphofructokinase-1 catalyzes the major rate-limiting step in glycolysis by converting fructose-6-phosphate to fructose-1,6-bisphosphate. It is not involved in gluconeogenesis or ketone production.

Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates for hepatic gluconeogenesis and ketone body formation.

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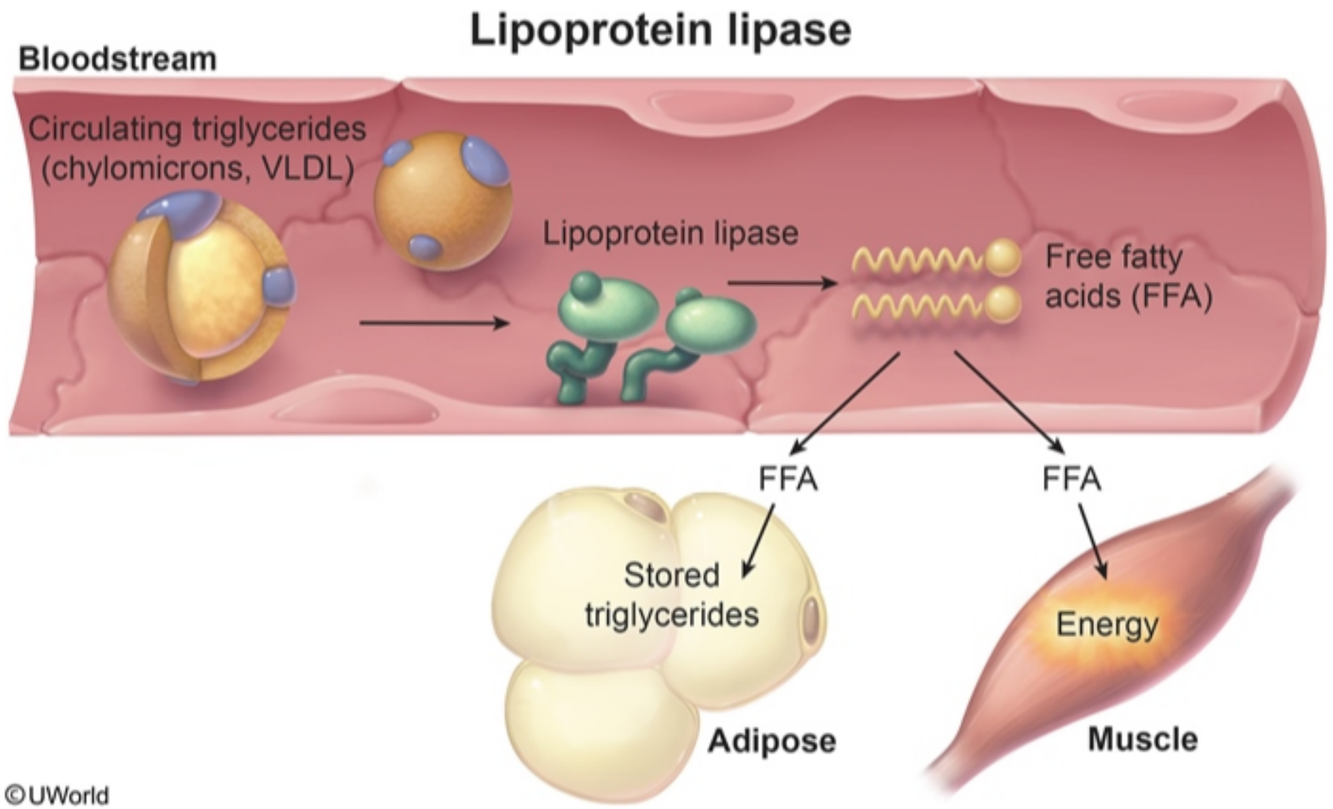

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References

- Lipolysis: more than just a lipase.

Biochemistry	Endocrine, Diabetes & Metabolism	Triglyceride metabolism
Subject	System	Topic

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A 47-year-old woman has a tumor that is causing symptoms of excessive hormone production. Surgical resection of the lesion is performed with no operative complications, and the neoplastic tissue is subjected to detailed pathologic studies. Electron microscopy reveals the tumor cells have highly developed, smooth endoplasmic reticulum. Which of the following is a possible direct effect of the substance secreted by these cells?

- A. Increase in water reabsorption in the renal collecting ducts
- B. Induction of hypoglycemia with increased cellular glucose uptake
- C. Promotion of male-pattern hair growth and virilization
- D. Stimulation of acid secretion from the gastric parietal cells
- E. Stimulation of milk production by the mammary tissue

Submit

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- A. Increase in water reabsorption in the renal collecting ducts (8%)
- B. Induction of hypoglycemia with increased cellular glucose uptake (10%)
- ✓ C. Promotion of male-pattern hair growth and virilization (63%)
- D. Stimulation of acid secretion from the gastric parietal cells (3%)
- E. Stimulation of milk production by the mammary tissue (12%)

Omitted
Correct answer
C

63%
Answered correctly

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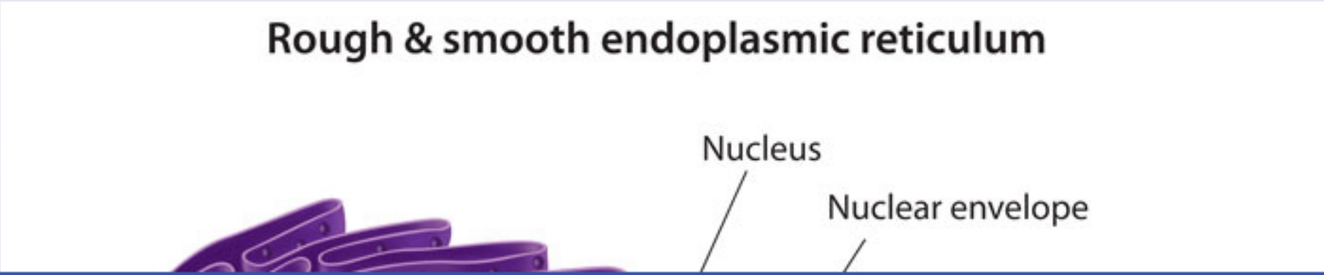
Time Spent

04/30/2020
Last Updated

Explanation



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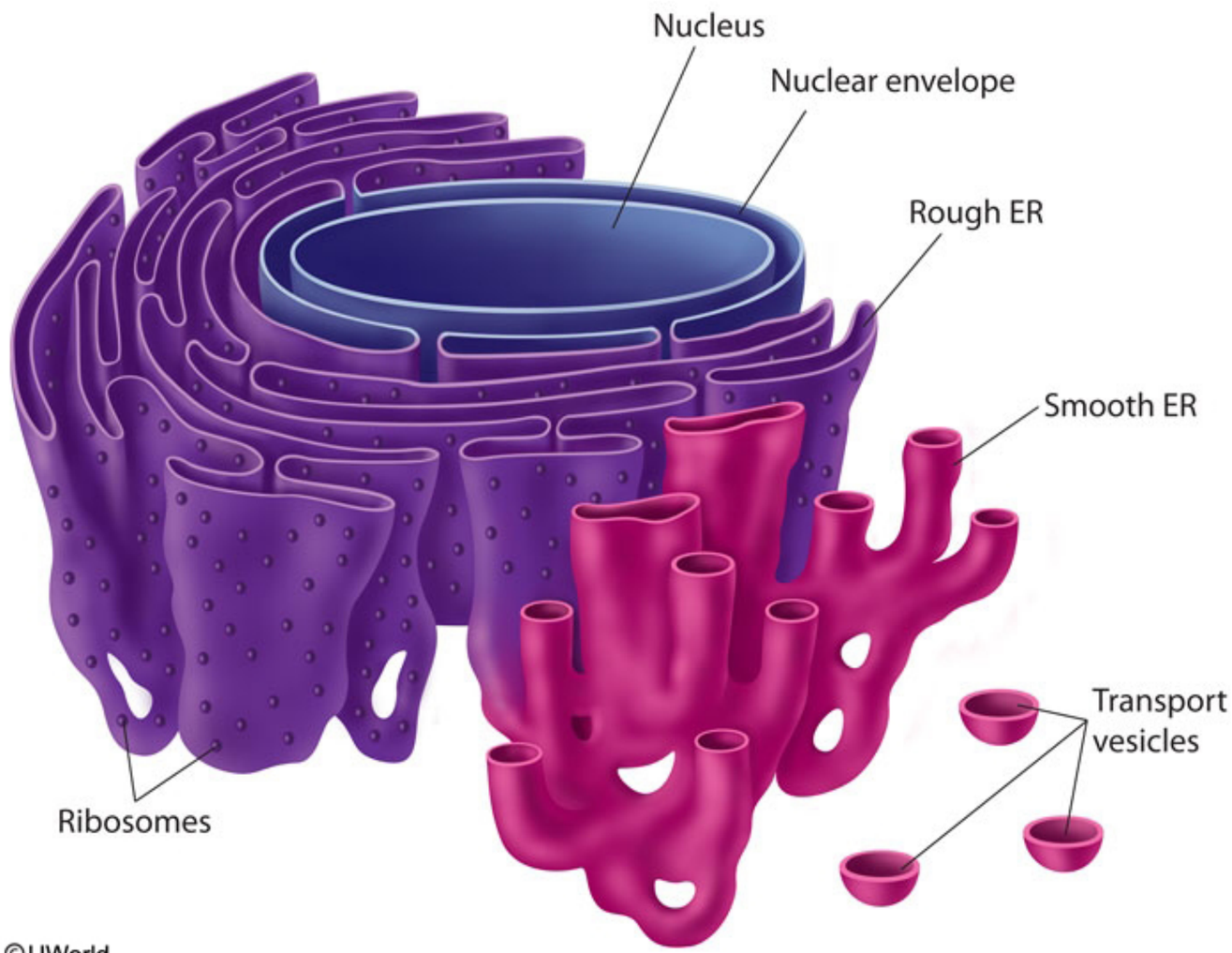
Rough & smooth endoplasmic reticulum



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The endoplasmic reticulum (ER) is an interconnected, membrane-bound network found in almost all eukaryotic cells. It is highly metabolically active and plays a significant role in the synthesis and modification of cellular components. The ER is recognizable on electron microscopy as a flattened tubular or laminar structure near or adjacent to the nucleus.

The **smooth endoplasmic reticulum** (SER) is involved in the synthesis and processing of hydrophobic compounds, including lipids, phospholipids, and cholesterol derivatives (eg, **steroid hormones**). Cholesterol is initially converted to pregnenolone in the mitochondria and then transferred to the SER, where the remaining steps of steroidogenesis occur. The SER contains the enzymes (eg, 21-hydroxylase) required for steroid and phospholipid biosynthesis. Steroid-producing cells (in the adrenals, gonads, and liver) characteristically contain a well-developed SER. This patient is likely experiencing **virilization** due to an **androgen-secreting** ovarian or adrenal **tumor**. Paraneoplastic syndromes can also occur due to overproduction of other sex steroids, cortisol (ie, Cushing syndrome), or aldosterone.

By contrast, the rough endoplasmic reticulum (RER) is characterized by numerous ribosomes on the outer membrane. The RER plays an important role in the synthesis and modification of targeted proteins, including secretable polypeptide hormones. Some of the clinically significant syndromes due to overproduction of **peptide hormones** by the RER include:

- Syndrome of inappropriate antidiuretic hormone (characterized by increased water reabsorption in the renal collecting ducts), often abbreviated SIADH, due to overproduction of vasopressin **(Choice A)**
- Hypoglycemia due to overproduction of insulin by certain pancreatic neuroendocrine tumors (insulinomas) **(Choice B)**
- Zollinger-Ellison syndrome (gastric acid hypersecretion and recurrent peptic ulcer) due to excess secretion of gastrin from pancreatic or small intestine gastrinomas **(Choice D)**
- Galactorrhea (pathologic mammary milk production) due to a prolactin-secreting lactotroph pituitary adenoma **(Choice E)**

Educational objective:
The initial step in the synthesis of steroid hormones is the conversion of cholesterol to pregnenolone in the mitochondria. The remainder of steroidogenesis occurs in the smooth endoplasmic reticulum. Steroid-producing cells contain a well-developed smooth endoplasmic reticulum.

References

- The endoplasmic reticulum: structure, function and response to cellular signaling.

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Biochemistry	Endocrine, Diabetes & Metabolism	Steroid hormones
Subject	System	Topic

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A 66-year-old man comes to the office due to progressive vision impairment over the last year that has begun to affect his ability to drive. He has difficulty reading road signs at night and reports excessive glare from the headlights of oncoming cars. The patient has a long history of hypertension and type 2 diabetes mellitus. Funduscopy reveals a diminished red reflex bilaterally with obscuration of retinal detail. It is determined that the patient's condition is in part due to intracellular accumulation of sorbitol. In healthy cells, this sugar alcohol is normally metabolized into which of the following substances to facilitate excretion?

- A. Fructose
- B. Galactitol
- C. Galactose
- D. Glucose
- E. Xylulose

Submit

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- ✓ A. Fructose (62%)
- B. Galactitol (16%)
- C. Galactose (6%)
- D. Glucose (8%)
- E. Xylulose (6%)

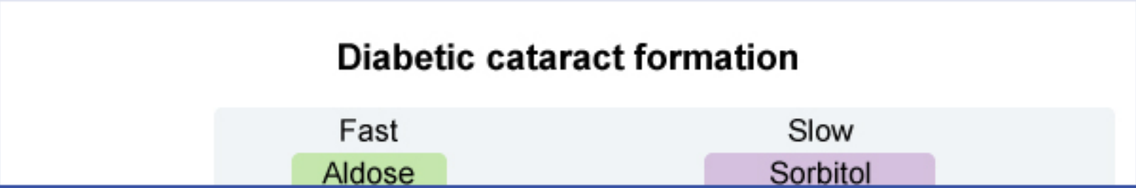
Omitted
Correct answer
A

62%
Answered correctly

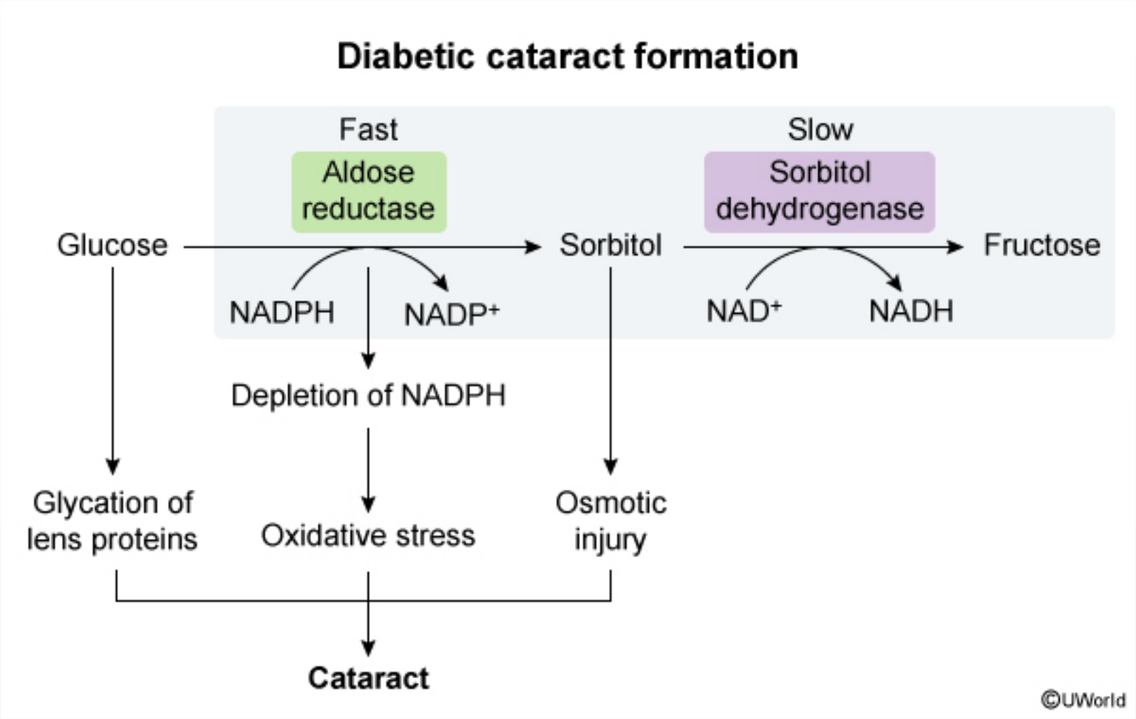
03 secs
Time Spent

04/22/2020
Last Updated

Explanation



Explanation



This patient has **cataracts**, a vision-impairing opacification of the lens that causes loss of the red reflex with decreased visualization of retinal details on ophthalmoscopic evaluation. The incidence of cataracts increases with **age**; other risk factors include smoking, excessive sunlight exposure, **diabetes mellitus**, and glucocorticoid use. In this patient, long-term hyperglycemia most likely contributed to cataract formation by causing **oversaturation of the polyol pathway**.

The first step in the polyol pathway (an alternative route of glucose metabolism) is the conversion of glucose into sorbitol by aldose reductase. Sorbitol cannot readily cross cell membranes and is therefore trapped inside the cells where it forms. The second enzyme in the pathway, sorbitol dehydrogenase, is able to **convert sorbitol into fructose** at a sufficient rate to prevent accumulation when glucose levels are normal. However, the process is slow; in long-standing hyperglycemia, sorbitol accumulates in tissues with lower sorbitol dehydrogenase activity, such as the retina.

Cataract

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Sorbitol accumulation increases cellular **osmotic and oxidative stress** and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy. In lens cells, the increased stress leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

(Choices B and C) Another function of aldose reductase is the conversion of galactose into galactitol (ie, this enzyme converts sugars into their corresponding sugar alcohols). Galactitol production via this pathway is normally insignificant. In galactosemia (galactose-1-phosphate uridyltransferase deficiency), an increased amount of galactitol is produced, resulting in congenital cataracts.

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted by the cells and taken up by the liver to produce glucose and triglycerides.

(Choice E) Xylulose is an intermediate in the pentose phosphate pathway, which is used to generate NADPH (for cholesterol and fatty acid synthesis) and ribose 5-phosphate (for nucleotide synthesis).

Educational objective:
In the polyol pathway, aldose reductase converts glucose into sorbitol, which is slowly metabolized into fructose by sorbitol dehydrogenase. Chronic hyperglycemia overwhelms this pathway, causing intracellular sorbitol accumulation and increased osmotic/oxidative stress. This accelerates cataract development in patients with diabetes, and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and

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References

- The sorbitol pathway in the human lens: aldose reductase and polyol dehydrogenase.
- Osmotic stress induced oxidative damage: possible mechanism of cataract formation in diabetes.
- Contribution of polyol pathway to diabetes-induced oxidative stress.

Biochemistry	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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An 18-year-old man comes to the office due to a progressive skin rash over the past year. He also has a long-standing history of an intermittent burning sensation in his palms and soles that is exacerbated by stress and fatigue. The burning sensation is particularly severe after exercise, during which the patient notes that he sweats minimally. Skin examination shows clusters of non-blanching, red papules in the gluteal, inguinal, and umbilical areas. Laboratory evaluation reveals an undetectable level of α-galactosidase A. Which of the following conditions is this patient at greatest risk for developing?

- A. Ataxia
- B. Hepatomegaly
- C. Neurofibrosarcoma
- D. Optic atrophy
- E. Renal failure

Submit

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A. Ataxia (13%)

B. Hepatomegaly (24%)

C. Neurofibrosarcoma (4%)

D. Optic atrophy (17%)

✓ E. Renal failure (40%)

Omitted
Correct answer
E

40%
Answered correctly

02 secs
Time Spent

01/22/2020
Last Updated

Explanation

Fabry disease	
	• X-linked recessive

Fabry disease	
Pathophysiology	• X-linked recessive • α-galactosidase A deficiency results in accumulation of globotriaosylceramide
Clinical features	• Neuropathic pain • Angiokeratomas • Telangiectasias • Glomerular disease (eg, proteinuria) • Cerebrovascular disease (eg, TIA, stroke) • Cardiac disease (eg, left ventricular hypertrophy)

TIA = transient ischemic attack.

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Fabry disease is an **X-linked recessive** lipid storage disorder characterized by **α-galactosidase A deficiency**. α-galactosidase A is a lysosomal enzyme responsible for the breakdown of **globotriaosylceramide (Gb3)**, a sphingolipid also known as ceramide trihexoside. Gb3 accumulation in vascular smooth muscle cells, glomerular/distal tubule cells, cardiac myocytes, and dorsal root and autonomic ganglia accounts for the adverse manifestations of Fabry disease.

The earliest symptoms present during adolescence and include **neuropathic pain** and **hypohidrosis** (decreased sweating). Small-fiber nerve involvement results in severe distal extremity pain and burning as well as distal loss of hot/cold temperature sensation. Exacerbating factors include exercise, stress, and fatigue. In late adolescence, **angiokeratomas** and **telangiectasias** develop on the skin. Angiokeratomas are dark red, non-blanching macules and papules that classically occur in clusters over the buttocks, groin, and umbilicus.

In early and mid-adulthood, **cerebrovascular** (eg, transient ischemic attack, stroke) and **cardiac** (eg, left ventricular hypertrophy) diseases develop and are the most common causes of death. In addition, Gb3 buildup in the **glomerulus and distal tubule** results in **proteinuria and polyuria**, respectively, and can progress to **renal failure** in the absence of enzyme replacement therapy.

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In early and mid-adulthood, **cerebrovascular** (eg, transient ischemic attack, stroke) and **cardiac** (eg, left ventricular hypertrophy) diseases develop and are the most common causes of death. In addition, Gb3 buildup in the **glomerulus and distal tubule** results in **proteinuria and polyuria**, respectively, and can progress to **renal failure** in the absence of enzyme replacement therapy.

(Choice A) Accumulation of cerebroside sulfate in metachromatic leukodystrophy (arylsulfatase A deficiency) causes progressive demyelination leading to ataxia, peripheral neuropathy, seizures, and hypotonia.

(Choice B) Hepatomegaly occurs in several lysosomal storage diseases. In Niemann-Pick disease, an accumulation of sphingomyelin also causes progressive neurodegeneration and cherry-red macular spots. In Hunter and Hurler syndromes, accumulation of heparan and dermatan sulfate results in developmental delay, skeletal abnormalities, and cardiac disease. In contrast, the liver is not typically affected in Fabry disease.

(Choice C) Neurofibrosarcomas are malignant peripheral nerve sheath tumors that arise from neurofibromas, which are soft, pink or flesh-colored, benign nerve sheath tumors often found on the trunk of patients with neurofibromatosis.

(Choice D) Optic atrophy, developmental regression, and seizures occur in Krabbe disease, a disorder characterized by galactocerebrosidase deficiency.

Educational objective:
In Fabry disease, α-galactosidase A deficiency causes accumulation of the sphingolipid globotriaosylceramide. The earliest manifestations of Fabry disease are neuropathic pain and angiokeratomas. Glomerular (eg, proteinuria, renal failure), cardiac (eg, left ventricular hypertrophy), and cerebrovascular (eg, transient ischemic attack, stroke) complications develop in adulthood.

polyuria, respectively, and can progress to **renal failure** in the absence of enzyme replacement therapy.

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References

- Renal complications of Fabry disease in children.
- Fabry nephropathy: a review – how can we optimize the management of Fabry nephropathy?
- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly.

Biochemistry	Endocrine, Diabetes & Metabolism	Fabry disease
Subject	System	Topic

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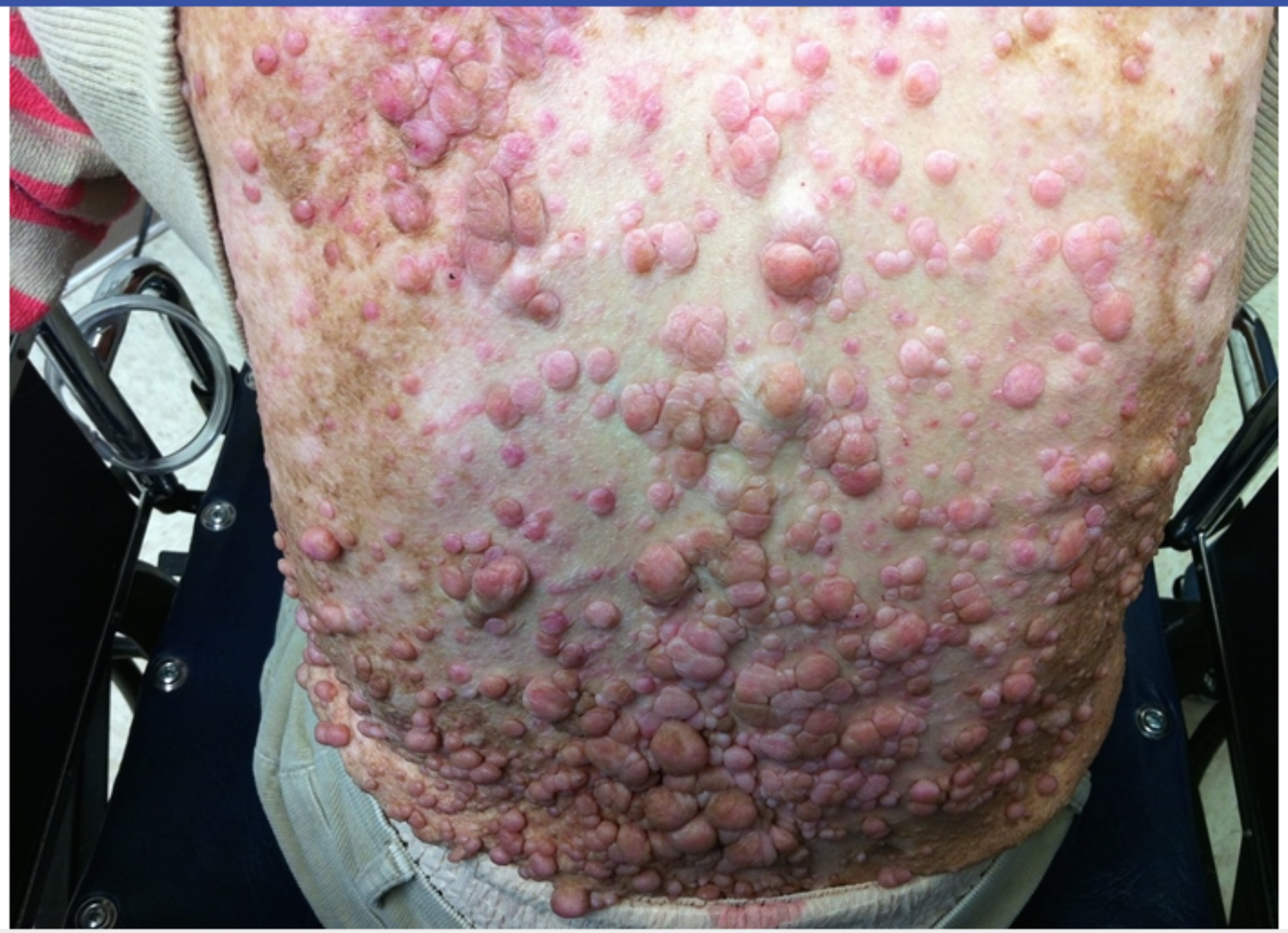
Exhibit Display



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A 1-day-old boy is diagnosed with hyperphenylalaninemia by newborn screening. He is placed on a special phenylalanine-restricted diet with tyrosine supplementation. The parents are extensively counseled on the boy's condition and informed of the necessary dietary restrictions. They are also instructed to return to his physician for regular follow-up visits. Several months later, laboratory test results indicate that the infant has a normal serum phenylalanine level. Careful examination, however, reveals some neurological abnormalities, including axial hypotonia and microcephaly. Further workup is notable for elevated prolactin, and his physician suspects a cofactor deficiency. Which of the following enzymes is most likely deficient in this patient?

A. Dihydrobiopterin reductase

B. Dopamine β-hydroxylase

C. Phenylalanine hydroxylase

D. Phenylethanolamine N-methyltransferase

E. Tyrosinase

Submit

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- ✓ A. Dihydrobiopterin reductase (50%)
- B. Dopamine β-hydroxylase (17%)
- C. Phenylalanine hydroxylase (14%)
- D. Phenylethanolamine N-methyltransferase (7%)
- E. Tyrosinase (10%)

Omitted
Correct answer
A

50%
Answered correctly

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Time Spent

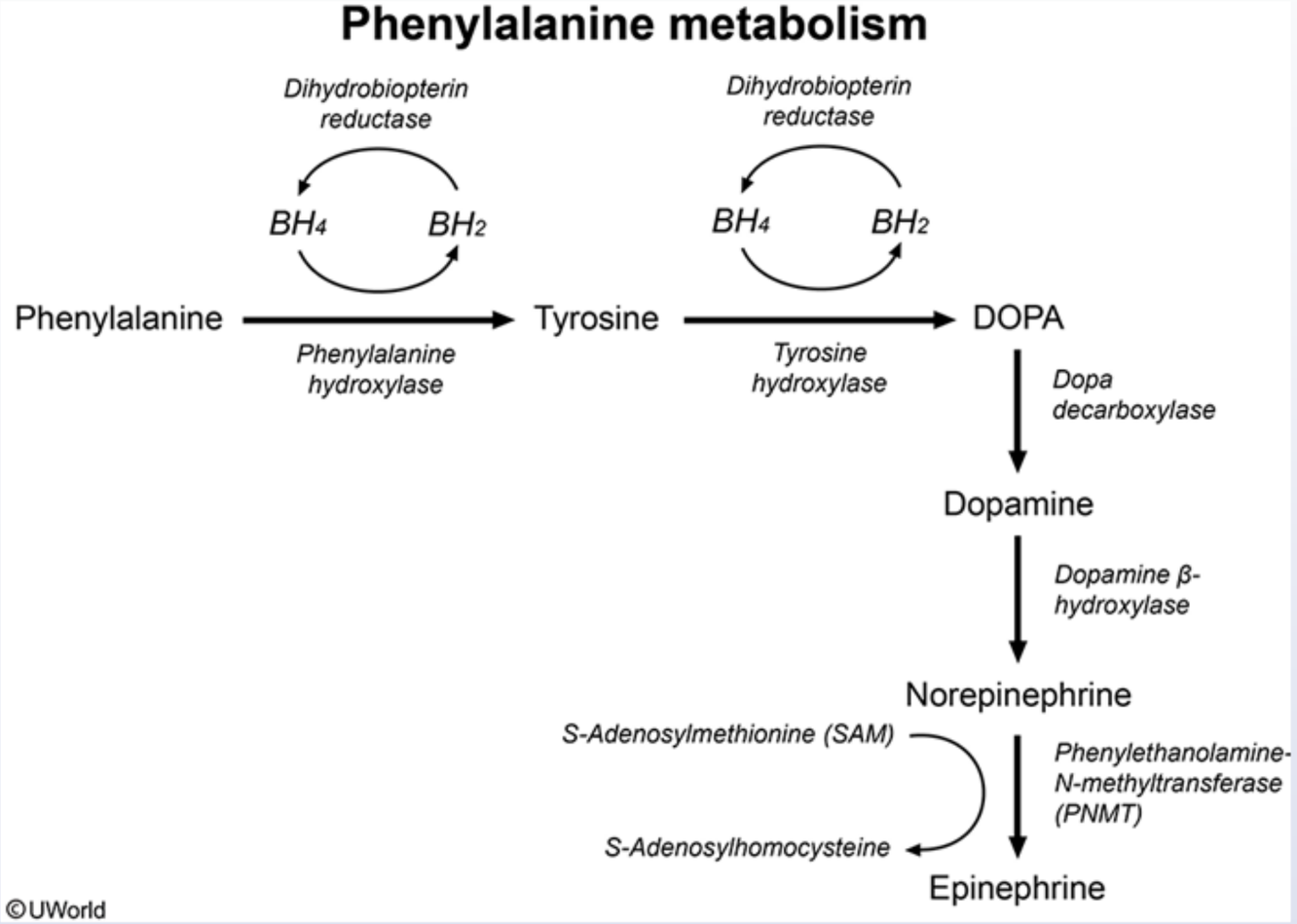
04/21/2020
Last Updated

Explanation

Phenylalanine metabolism

Dihydrobiopterin reductase

Dihydrobiopterin reductase



This patient with phenylketonuria (PKU) most likely has a deficiency of dihydrobiopterin reductase (reduces BH_2 to BH_4) based on the combination of **hyperphenylalaninemia** and **elevated prolactin**. Phenylalanine is converted to tyrosine by phenylalanine hydroxylase using BH_4 as a cofactor. Tyrosine is converted to DOPA via the enzyme tyrosine hydroxylase, which also uses BH_4 as a cofactor. Once DOPA is synthesized, it is decarboxylated to dopamine by DOPA decarboxylase. Dopamine ultimately serves as the precursor molecule to the catecholamines

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In classic PKU, supplementation of tyrosine allows for normal catecholamine production due to intact function of tyrosine hydroxylase. However, deficiency of **dihydrobiopterin reductase** results in both **hyperphenylalaninemia** from impaired phenylalanine hydroxylase activity and **low dopamine** levels from impaired tyrosine hydroxylase activity. Although phenylalanine levels can be controlled by dietary restriction, downstream deficiencies of neurotransmitters (eg, dopamine, norepinephrine, epinephrine, serotonin) lead to progressive neurologic deterioration in these patients. Normally, dopamine from the tuberoinfundibular system tonically inhibits prolactin release. Decreased BH_4 causes lower levels of dopamine, resulting in **increased prolactin** levels.

(Choice B) The enzyme dopamine β-hydroxylase catalyzes the biosynthesis of norepinephrine from dopamine. It does not use BH_4 as a cofactor.

(Choice C) Phenylalanine hydroxylase deficiency is the most common cause of PKU. This patient's phenylalanine levels have normalized with dietary therapy, but he has low dopamine levels (as indicated by elevated prolactin). Patients with classic PKU or phenylalanine hydroxylase deficiency do not have any difficulty producing dopamine with adequate levels of dietary tyrosine.

(Choice D) Phenylethanolamine N-methyltransferase (PNMT) converts norepinephrine to epinephrine. It requires S-adenosyl-methionine (SAM) as a cofactor.

(Choice E) Tyrosinase deficiency causes albinism, characterized by a lack of pigment in skin and hair due to absent melanin production. Melanin is synthesized in melanocytes from tyrosine by tyrosinase.

Educational objective:
Dihydrobiopterin reductase deficiency results in impaired tetrahydrobiopterin (BH_4) levels. BH_4 is an important cofactor for both phenylalanine hydroxylase and tyrosine hydroxylase. Although phenylalanine levels can be corrected with dietary restriction, downstream deficiencies of dopamine, norepinephrine, epinephrine, and serotonin lead to progressive neurologic deterioration.

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References

- Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain.
- Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies.
- Serum prolactin as a tool for the follow-up of treated DHPR-deficient patients.

Biochemistry	Endocrine, Diabetes & Metabolism	Phenylketonuria
Subject	System	Topic

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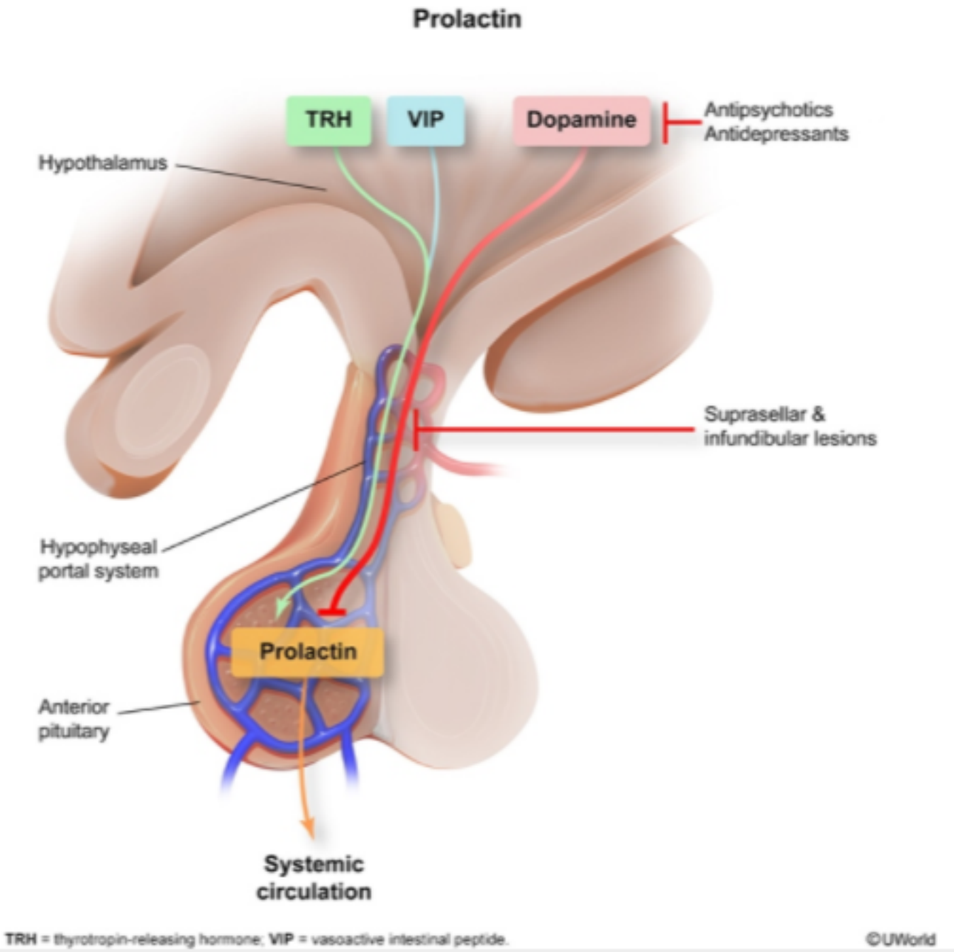
This patient with phenylketonuria (PKU) most likely has a deficiency of dihydrobiopterin reductase (reduces BH_2 to BH_4) based on the combination

Exhibit Display



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A 5-year-old girl is brought to the clinic due to several months of fatigue and difficulty walking. She ambulates normally at first but rapidly becomes weak and tired. The patient has not been ill recently and is usually happy and playful. She has a history of mild motor delays but is otherwise developmentally normal. Vital signs are within normal limits. Examination shows mildly decreased power in all extremities but no ataxia. Cardiac auscultation reveals a 1/6 systolic murmur and an S3 gallop. Laboratory results are as follows:

Serum chemistry	
Glucose	37 mg/dL
Creatine kinase	304 U/L
Urinalysis	
Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

A. Acetoacetate
B. Arachidonic acid
C. Glutathione
D. Homocysteine

Glucose	37 mg/dL
Creatine kinase	304 U/L

Urinalysis

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Submit

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Creatine kinase	304 U/L

Urinalysis

Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

- ✓ A. Acetoacetate (44%)
- B. Arachidonic acid (3%)
- C. Glutathione (6%)
- D. Homocysteine (8%)
- E. Lactate (8%)
- F. Palmitate (27%)

Omitted
Correct answer

44%
Answered correctly

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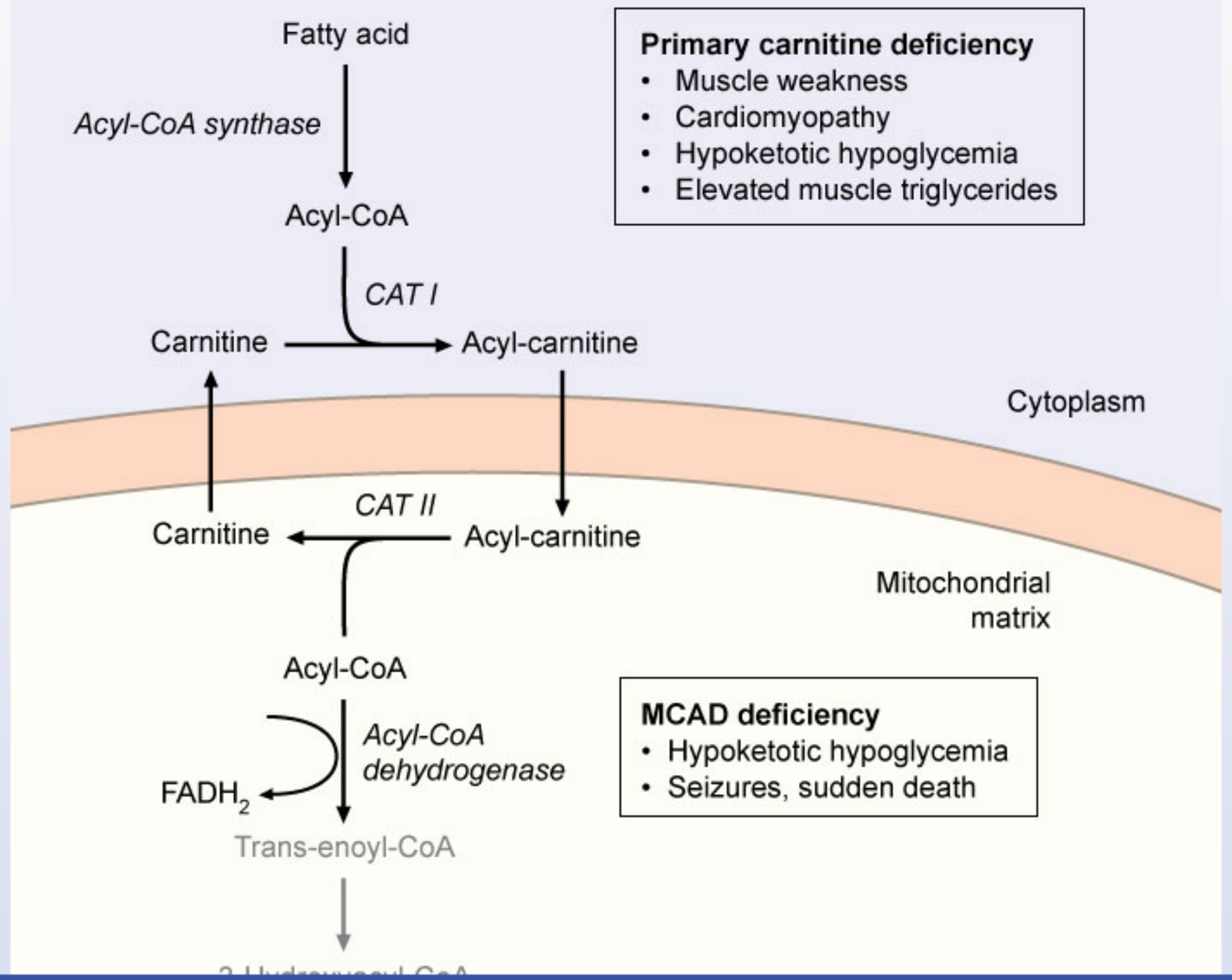
Time Spent

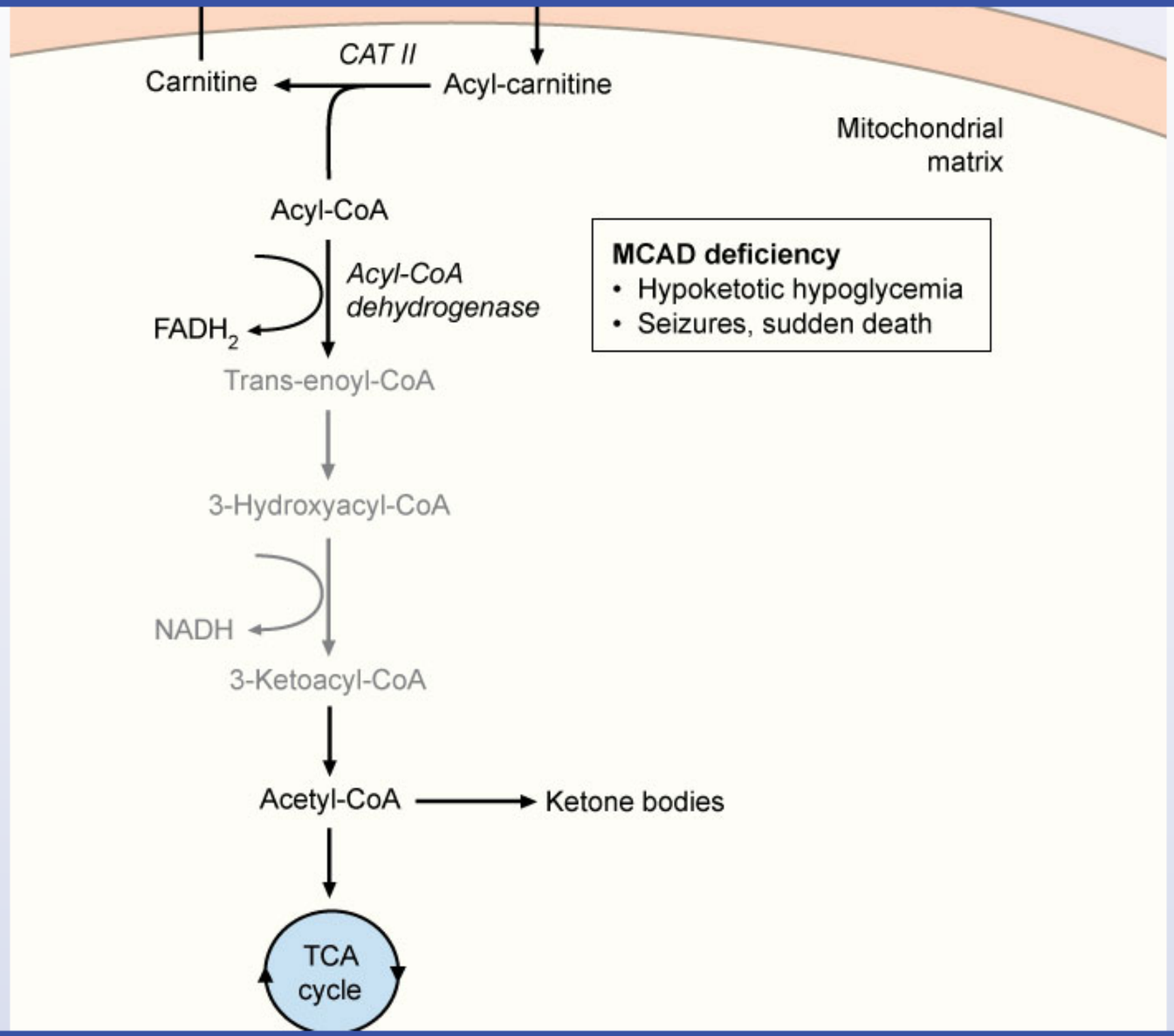
03/08/2020
Last Updated

Fatty acid oxidation



Primary carnitine deficiency
- Muscle weakness
- Cardiomyopathy
- Hypoketotic hypoglycemia
- Elevated muscle triglycerides

MCAD deficiency
- Hypoketotic hypoglycemia
- Seizures, sudden death


CAT II
Carnitine
Acyl-carnitine
Mitochondrial matrix
Acyl-CoA
Acyl-CoA dehydrogenase
FADH2
Trans-enoyl-CoA
3-Hydroxyacyl-CoA
NADH
3-Ketoacyl-CoA
Acetyl-CoA
Ketone bodies
TCA cycle
MCAD deficiency
• Hypoketotic hypoglycemia
• Seizures, sudden death

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This patient's myopathy (eg, elevated creatine kinase, weakness), cardiomyopathy (eg, S3 gallop), and **hypoketotic hypoglycemia** (eg, absence of ketones in the urine) in the setting of **decreased muscle carnitine** content is consistent with **primary carnitine deficiency**. The condition is caused by a defect in the protein responsible for carnitine transport across the mitochondrial membrane. Without sufficient carnitine, fatty acids cannot be transported from the cytoplasm into the mitochondria as acyl-carnitine (carnitine shuttle). The mitochondria therefore cannot β-oxidize the fatty acids into acetyl CoA, the carbon substrate for the citric acid cycle. As a result, cardiac and skeletal myocytes cannot generate ATP from fatty acids (leading to muscle weakness, cardiomyopathy) and the liver is unable to synthesize **ketone bodies** (manifests as hypoketotic hypoglycemia).

Hypoketotic hypoglycemia is also seen in other fatty acid oxidation disorders (eg, acyl CoA dehydrogenase deficiency).

(Choice B) Arachidonic acid can be ingested or synthesized from phospholipids in the cell membrane. Its eicosanoid derivatives (eg, prostanoids, leukotrienes) are important modulators of inflammation. It is not affected by carnitine levels.

(Choice C) Glutathione is a tripeptide that can be synthesized from amino acids (glutamate, cysteine, and glycine). It is an important antioxidant and plays a role in DNA synthesis and repair.

(Choice D) Homocysteine is an amino acid that is synthesized from methionine. Using vitamin cofactors, it can be converted to cysteine (pyridoxine) or recycled into methionine (cobalamin).

(Choice E) Lactate is produced from pyruvate under anaerobic conditions. Patients with carnitine deficiency synthesize lactate normally but may produce increased lactate during times of catabolic stress due to inability to utilize fatty acids for energy production.

(Choice F) Palmitate is a fatty acid that can be ingested or synthesized from carbohydrates. Palmitate synthesis occurs in the cytosol and would not be affected by carnitine deficiency.

Educational objective:
Carnitine deficiency impairs fatty acid transport from the cytoplasm into mitochondria, preventing β-oxidation of fatty acids into acetyl CoA. This leads to cardiac and skeletal myocyte injury (lack of ATP from citric acid cycle) and impaired ketone body production by the liver during fasting periods.

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References

- Primary carnitine deficiency: novel mutations and insights into the cardiac phenotype.
- Systemic primary carnitine deficiency: an overview of clinical manifestations, diagnosis, and management.

Biochemistry	Endocrine, Diabetes & Metabolism	Beta oxidation
Subject	System	Topic

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A 4-month-old boy is brought to the office for his first visit since arriving in the United States. The patient was recently adopted, and his adoptive mother says the boy is tremulous compared to her biological children. Over the past week, the boy has also had episodes of upward eye deviation and bilateral arm and leg shaking for approximately 2 minutes at a time. Biological family history is not available. His temperature is 36.7 C (98.1 F), blood pressure is 90/40 mm Hg, pulse is 120/min, and respirations are 30/min. Examination shows a fair-skinned infant with blue eyes and a musty body odor. Which of the following amino acids is most likely essential in this patient?

- A. Cysteine
- B. Isoleucine
- C. Leucine
- D. Phenylalanine
- E. Tyrosine
- F. Valine

Submit

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- A. Cysteine (4%)
- B. Isoleucine (0%)
- C. Leucine (1%)
- D. Phenylalanine (17%)
- ✓ E. Tyrosine (74%)
- F. Valine (0%)

Omitted
Correct answer
E

74%
Answered correctly

02 secs
Time Spent

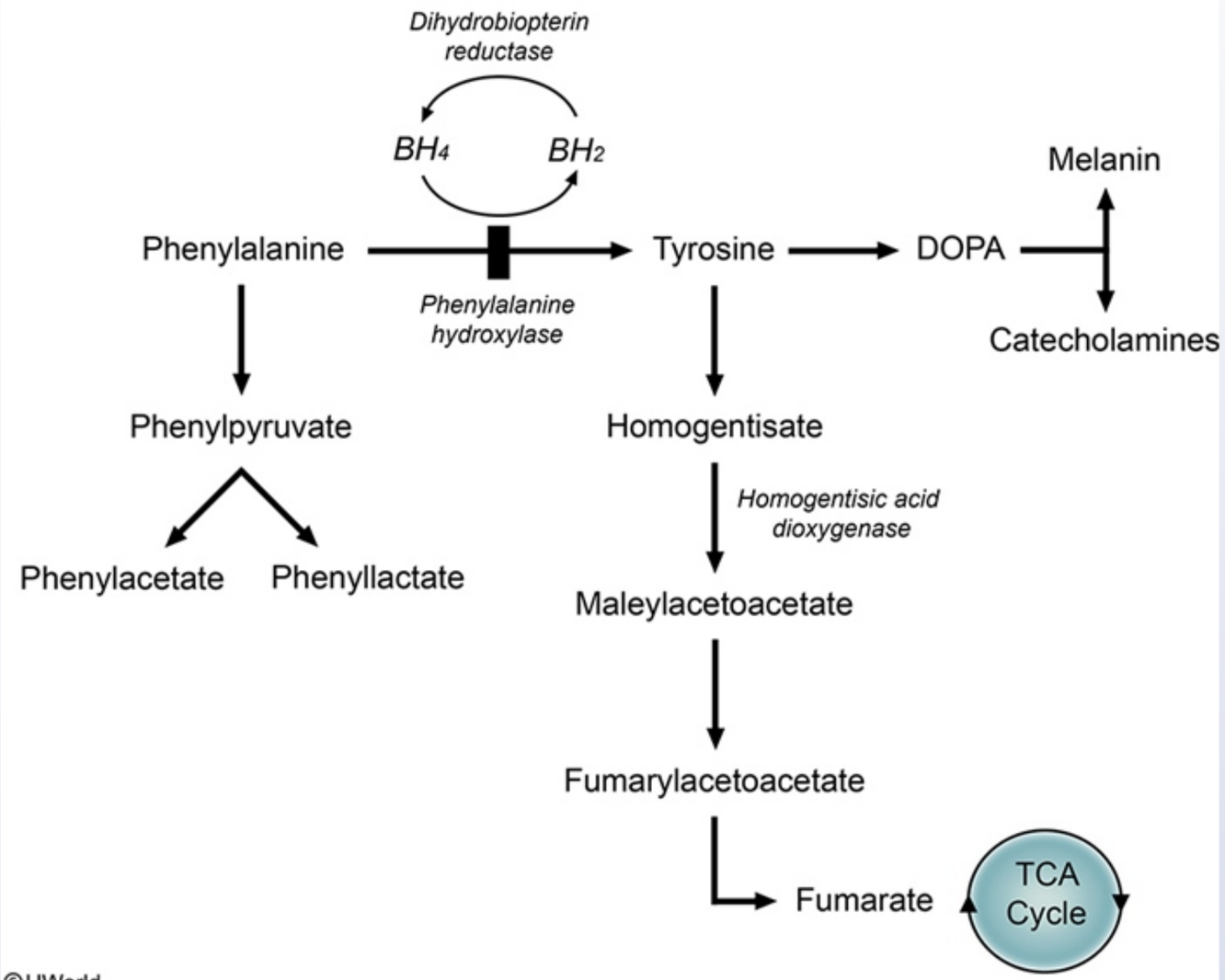
04/26/2020
Last Updated

Explanation

Phenylketonuria

Dihydrobiopterin

Phenylketonuria



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This patient's clinical presentation suggests phenylketonuria (PKU). Classic PKU (the most common form) occurs most frequently in persons of Scandinavian descent. Individuals who are homozygous for this **autosomal recessive** disorder have a severe **deficiency** of **phenylalanine hydroxylase**, the enzyme responsible for conversion of phenylalanine to tyrosine. Tyrosine becomes an essential amino acid in these patients as it cannot be synthesized from phenylalanine, although most patients receive adequate amounts in their diet and do not require supplementation. Furthermore, the excess phenylalanine inhibits tyrosinase, which normally results in the downstream production of melanin. The lack of melanin causes the **fair complexion** seen in this patient.

Although development is initially normal, most untreated patients develop **intellectual disability** by age 6 months. Other classic findings include **seizures**, eczema, light hair/skin pigmentation, and a "**musty**," odor. However, cognitive impairment can be lessened by early detection (newborn screening) and **restriction of phenylalanine intake**.

(Choice A) Cystinuria is due to impaired transport of renal cystine (a homodimer of cysteine), which leads to cystine renal stone formation. Clinical manifestations typically include flank pain, hematuria, and possible stone passage in children or adolescents.

(Choices B, C, and F) The branched-chain amino acids (leucine, isoleucine, valine) are elevated in maple syrup urine disease, an amino acid disorder marked by deficiency of branched-chain alpha-ketoacid dehydrogenase complex. Buildup of the branched-chain amino acids and their metabolites is toxic, leading to feeding difficulties, seizures, cerebral edema, and a sweet odor of the urine.

(Choice D) Phenylalanine levels are significantly elevated in PKU, leading to neurologic defects. Therapy depends on dietary restriction of phenylalanine.

Educational objective:
Phenylketonuria (PKU) results from an inability to convert phenylalanine to tyrosine by the phenylalanine hydroxylase system, making tyrosine an essential amino acid in these patients. Classic clinical features of untreated PKU include intellectual disability, seizures, light pigmentation, and a "musty" odor.

References

- Phenylalanine hydroxylase deficiency: diagnosis and management guideline.

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A 2-year-old boy is brought to the emergency department with fever, vomiting, and sleepiness. He had several episodes of emesis this morning, and his mother was unable to wake him from his afternoon nap. The boy has had mild rhinorrhea and fever for the past 3 days. Since the newborn period, the parents say that the patient has had multiple illnesses characterized by vomiting and sleepiness. Prior laboratory testing revealed increased blood ammonia levels during these episodes and markedly increased orotic acid excretion in the urine. Physical examination shows a tachypneic boy who is unresponsive to all stimuli. Which of the following enzymes is most likely to be deficient in this patient?

A. Carbamoyl phosphate synthetase I

B. Hypoxanthine-guanine phosphoribosyltransferase

C. N-acetylglutamate synthetase

D. Ornithine transcarbamylase

E. Uridine monophosphate synthetase

Submit

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- A. Carbamoyl phosphate synthetase I (15%)
- B. Hypoxanthine-guanine phosphoribosyltransferase (4%)
- C. N-acetylglutamate synthetase (3%)
- ✓ D. Ornithine transcarbamylase (64%)
- E. Uridine monophosphate synthetase (11%)

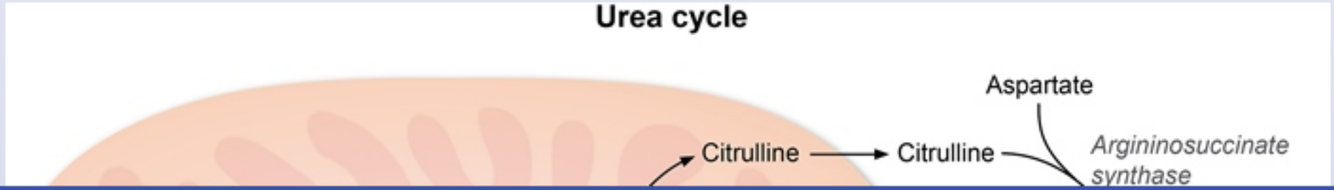
Omitted
Correct answer
D

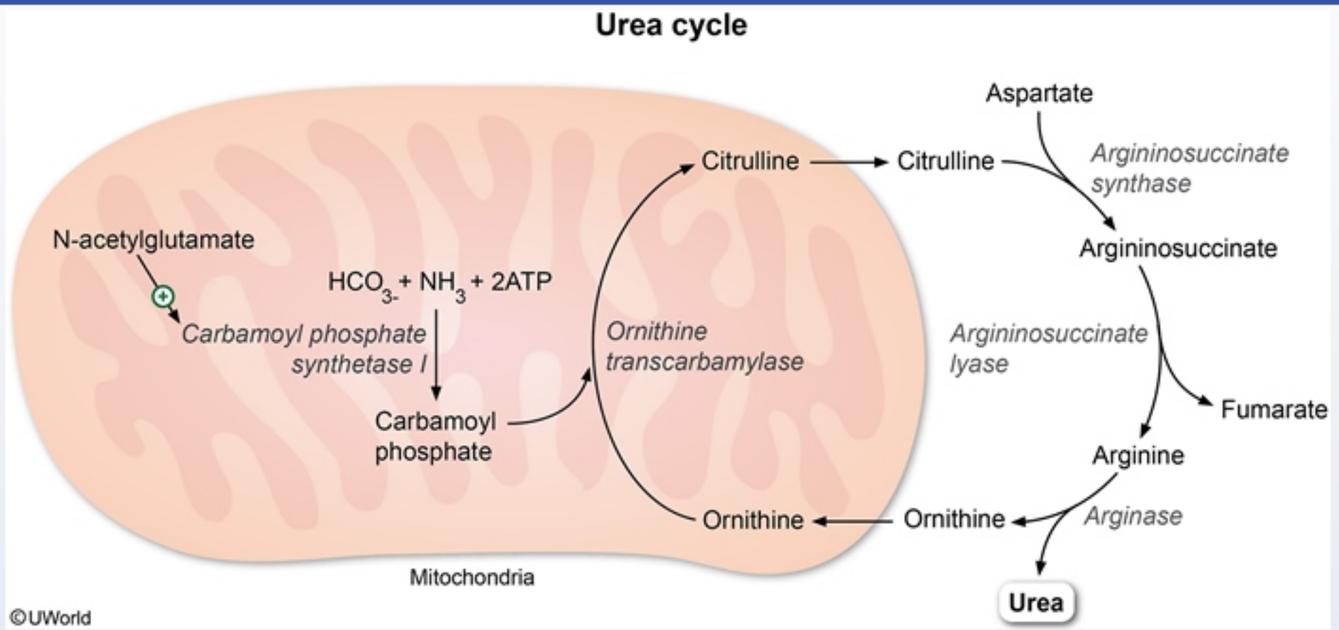
64%
Answered correctly

03 secs
Time Spent

03/08/2020
Last Updated

Explanation





Ammonia generated from the metabolism of amino acids is converted into urea by the urea cycle. The combination of bicarbonate (HCO_3-), ammonia, and ATP is catalyzed by carbamoyl phosphate synthetase (rate-limiting enzyme in the urea cycle) to yield carbamoyl phosphate. Carbamoyl phosphate combines with ornithine to form citrulline in a reaction catalyzed by ornithine transcarbamylase. Citrulline enters the cytosol and is converted to argininosuccinate, which is then converted to arginine. The conversion of arginine to ornithine by arginase completes the urea cycle by releasing a urea molecule. N-acetylglutamate serves as a regulator of the urea cycle through activation of carbamoyl phosphate synthetase I.

This patient most likely has **ornithine transcarbamylase (OTC) deficiency**, the most common urea cycle disorder. OTC deficiency results in excess carbamoyl phosphate, which stimulates pyrimidine synthesis. As an intermediate product in this pathway, orotic acid accumulates and results in **increased urinary orotic acid**.

Patients also have **hyperammonemia** due to impaired ammonia excretion, which is a **metabolic emergency**. Ammonia is neurotoxic and causes **episodes of vomiting and confusion/coma**. **Tachypnea** also occurs due to cerebral edema from ammonia buildup, resulting in central

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Patients also have **hyperammonemia** due to impaired ammonia excretion, which is a **metabolic emergency**. Ammonia is neurotoxic and causes **episodes of vomiting and confusion/coma**. **Tachypnea** also occurs due to cerebral edema from ammonia buildup, resulting in central hyperventilation and respiratory alkalosis. Metabolic decompensation is often triggered by illness (eg, viral upper respiratory infection, acute otitis media), fasting, or increased protein intake.

(Choices A and C) Although defects in carbamoyl phosphate synthetase I and N-Acetylglutamate synthetase also result in hyperammonemia, levels of carbamoyl phosphate are low and orotic acid is not elevated in the urine.

(Choice B) Hypoxanthine-guanine phosphoribosyltransferase deficiency (Lesch-Nyhan syndrome) results in hyperuricemia because purines cannot be salvaged from degraded DNA. Urate kidney stones and self-mutilation are classic clinical manifestations.

(Choice E) Uridine monophosphate synthetase (UMPS) is part of the pyrimidine synthesis pathway. UMPS deficiency leads to orotic acid buildup (similar to OTC deficiency) but not hyperammonemia. Characteristic findings include megaloblastic anemia and delayed growth.

Educational objective:
Patients with urea cycle disorders typically have discrete episodes of vomiting, tachypnea, and confusion/coma secondary to hyperammonemia (a metabolic emergency). Ornithine transcarbamylase deficiency is the most common disorder of the urea cycle and is characterized by hyperammonemia and elevated urinary orotic acid.

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References

- Ornithine Transcarbamylase Deficiency.
- Urea Cycle Disorders Overview.

Biochemistry	Endocrine, Diabetes & Metabolism	Urea cycle
Subject	System	Topic

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A 23-year-old apparently healthy man who recently immigrated to the United States comes to an outpatient clinic to establish care. When asked about his past medical history, he says that he has no significant medical problems. However, his mother told him that he was born with "a problem metabolizing sugar." The patient maintains no dietary restrictions and regularly eats vegetables, fruits, meats, and processed foods. Urine samples show a repeatedly positive copper reduction test, but glucose oxidase dipstick testing is negative. Which of the following enzymes is most likely to be deficient in this patient?

A. Acid α-glucosidase

B. Aldolase B

C. Fructokinase

D. Galactose-1-phosphate uridyl transferase

E. Lactase

Submit

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- A. Acid α-glucosidase (8%)
- B. Aldolase B (12%)
- ✓ C. Fructokinase (62%)
- D. Galactose-1-phosphate uridyl transferase (10%)
- E. Lactase (6%)

Omitted
Correct answer
C

62%
Answered correctly

04 secs
Time Spent

04/26/2020
Last Updated

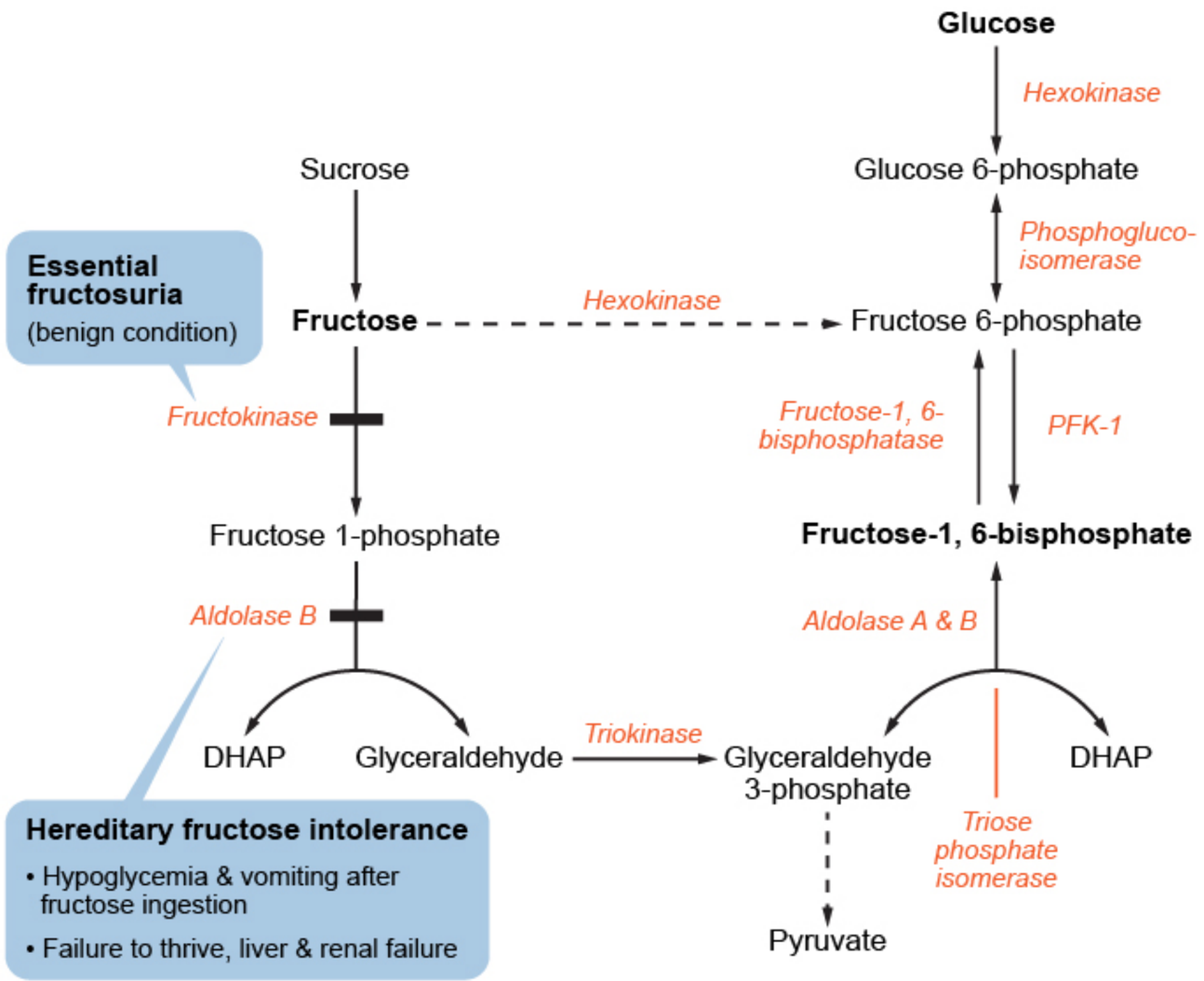
Explanation

Disorders of fructose metabolism

Glucose

Hexokinase

Disorders of fructose metabolism



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This asymptomatic patient with history of an inborn error of sugar metabolism most likely has **essential fructosuria**. This benign, autosomal recessive disorder causes some of the dietary fructose load to be secreted in the urine unchanged due to defective metabolism by **fructokinase**. Fructose, similar to glucose and galactose, is a **reducing sugar** and can be detected by a **copper reduction test**, which nonspecifically detects the presence of reducing sugar. A urine dipstick, however, uses glucose oxidase to ascertain the presence of urinary glucose and will not test positive in the presence of fructose or galactose.

(Choice A) Acid α-glucosidase (or acid maltase) deficiency causes glycogen storage disease type II (Pompe disease). Affected infants have cardiomyopathy, muscle weakness, and hypotonia.

(Choice B) Aldolase B deficiency is a life-threatening disorder caused by the inability to metabolize fructose-1-phosphate (a toxic intermediate that accumulates in cells and depletes intracellular phosphate). Patients become acutely symptomatic after ingesting fructose-containing foods and eventually develop liver failure. Treatment includes elimination of dietary fructose.

(Choice D) Galactosemia is an autosomal recessive disorder caused by galactose-1-phosphate uridyl transferase deficiency. It is characterized by neonatal jaundice, vomiting, cataract formation, hepatomegaly, and failure to thrive. Treatment includes elimination of all milk products from the diet and feeding with soy-based infant formula.

(Choice E) Lactase is a mucosal enzyme responsible for the digestion of lactose. Acquired lactase deficiency is the most common cause of selective carbohydrate malabsorption. Patients with lactase deficiency experience gastrointestinal symptoms (eg, bloating, diarrhea) following the ingestion of dairy products.

Educational objective:
Unlike hereditary fructose intolerance (aldolase B deficiency) and classic galactosemia (galactose-1-phosphate uridyl transferase deficiency), essential fructosuria (fructokinase deficiency) is a benign disorder. Although affected patients are asymptomatic, their urine will test positive for a reducing sugar due to the presence of unmetabolized fructose.

Biochemistry	Endocrine, Diabetes & Metabolism	Fructose metabolism
Subject	System	Topic

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Biochemistry	Endocrine, Diabetes & Metabolism	Fructose metabolism
Subject	System	Topic

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A 34-year-old man is admitted to the hospital after sustaining a head injury and fractures of both femurs in a motor vehicle collision. CT scan of the head reveals a left-sided extradural hematoma. He has no history of chronic illness and takes no medications. The patient receives intravenous fluid boluses and blood transfusions and is taken to the operating room for fracture repair and removal of the hematoma. On the first postoperative day, laboratory results show high plasma glucose and lactate levels. Which of the following is the primary contributor to this patient's elevated blood glucose levels?

A. Administration of intravenous fluid boluses
B. Decreased hepatic glycerol supply
C. Increased anaerobic glycolysis
D. Increased hepatic glucose production
E. Increased renal gluconeogenesis

Submit

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- A. Administration of intravenous fluid boluses (9%)
- B. Decreased hepatic glycerol supply (2%)
- C. Increased anaerobic glycolysis (19%)
- ✓ D. Increased hepatic glucose production (64%)
- E. Increased renal gluconeogenesis (4%)

Omitted
Correct answer
D

64%
Answered correctly

01 sec
Time Spent

05/14/2020
Last Updated

Explanation

Stress hyperglycemia	
Presentation	• Transient hyperglycemia without known diabetes
	• Hemorrhage, major trauma

Stress hyperglycemia	
Presentation	• Transient hyperglycemia without known diabetes
Risk factors	• Hemorrhage, major trauma • Hypoxia • Sepsis
Pathogenesis	• Secretion of cortisol, catecholamines, glucagon & proinflammatory cytokines • Increased hepatic glycogenolysis & gluconeogenesis

Stress hyperglycemia is a transiently elevated blood glucose level in the context of severe illness in patients without preexisting diabetes mellitus. It is common in the intensive care unit and is typically seen in those with sepsis and other severe infections, burns, trauma, or major hemorrhage.

Severe metabolic stress is associated with increased production of **cortisol**, **catecholamines** (primarily epinephrine and norepinephrine), glucagon, and proinflammatory cytokines (eg, IL-1, IL-6, tumor necrosis factor-alpha). Cortisol, catecholamines, and glucagon act on the liver to **increase glycogenolysis and gluconeogenesis**, stimulating release of glucose from the liver into the blood.

In addition, the release of proinflammatory cytokines is associated with increased expression of glucose transporter (GLUT) 1 in the CNS and macrophages, along with decreased expression of GLUT4 (which mediates insulin-induced glucose uptake in peripheral tissues). This facilitates **increased glucose uptake by the brain** and **immune cells** responsible for fighting infection.

(Choice A) During trauma resuscitation, most patients are given isotonic fluids (eg, normal saline, Ringer lactate), which are unlikely to cause hyperglycemia. Even if mild fluid-induced hyperglycemia occurs, blood glucose levels typically normalize quickly after fluid boluses.

(Choice B) Norepinephrine stimulates peripheral lipolysis, releasing glycerol, which can be taken up by the liver for use in gluconeogenesis. Therefore, stress increases, not decreases, the hepatic glycerol supply.

(Choice C) Severe illness is often associated with increased anaerobic glycolysis due to systemic or local tissue hypoxia (blood loss in this patient). Increased conversion of glucose to lactate in ischemic tissues *raises plasma lactate levels*. Glucose levels are often concurrently

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(Choice E) The renal cortex can convert lactate to glucose via gluconeogenesis. However, it makes a significantly smaller contribution to circulating glucose levels than hepatic gluconeogenesis.

Educational objective:
Stress hyperglycemia is transiently elevated blood glucose levels in the context of severe illness (eg, sepsis, burns, major hemorrhage) in patients without preexisting diabetes mellitus. Cortisol and catecholamines released in response to severe metabolic stress act on the liver to increase glycogenolysis and gluconeogenesis.

References

- Stress hyperglycemia: an essential survival response!

Biochemistry Endocrine, Diabetes & Metabolism Diabetes mellitus

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Biochemistry	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

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